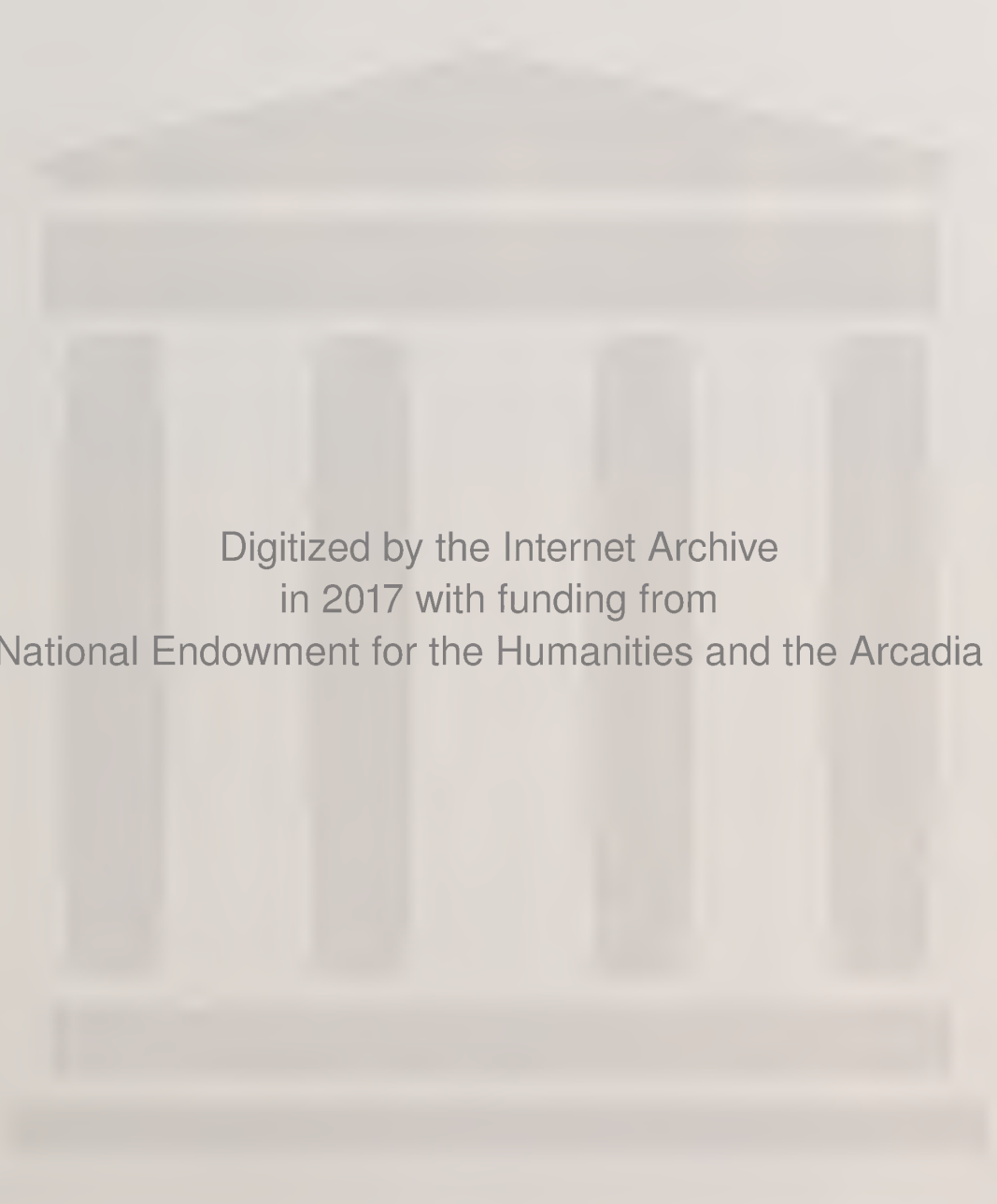
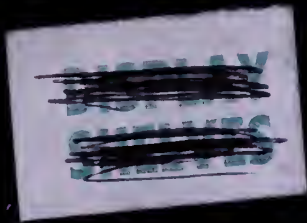


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BOLETIN

ASOCIACION MEDICA DE PUERTORICO

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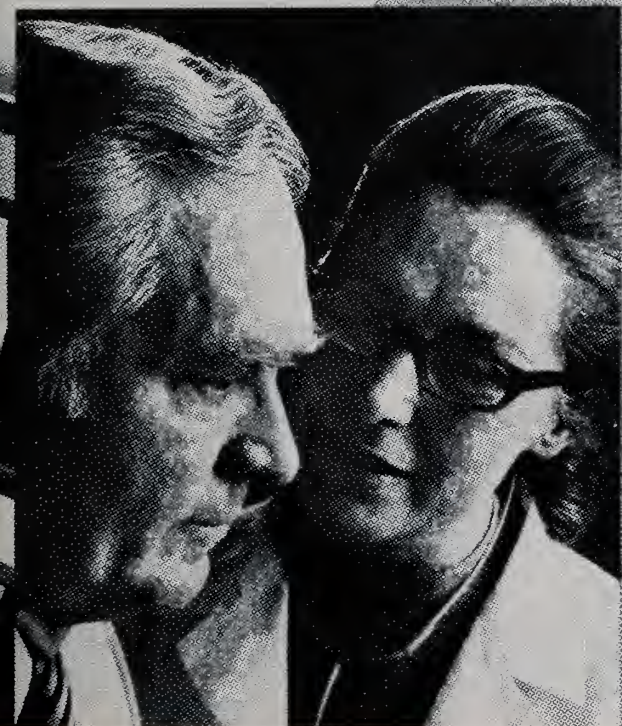
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Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Contact Dermatitis Can Be Controlled

Skin Rash Is Pesky

Your doctor calls it allergic contact dermatitis.

You call it a skin rash.

By either name it's a Big Itch. It's caused by something that rubs against your skin. And it won't go away until the offending substance is identified and removed.

Almost everything can occasionally cause allergic contact dermatitis in someone. And, to further complicate matters, you may be in contact with the substance for years and years with no problem, only to suddenly become allergic and develop a rash.

The metal nickel causes rash in many individuals. There is nickel in medallions, zippers, identification tags and necklaces, in hairpins and curlers, and in thimbles, needles, scissors, coins and pens. Nickel-plated earrings often produce one of the cardinal signs of nickel sensitivity in women

— earlobe rash, says a pamphlet from the American Medical Association.

Rubber is a frequent offender. Not natural rubber, but the various chemicals that are added to rubber to preserve it and enhance its qualities. There is rubber in various foundation garments, swim suits, surgical bandages and support hose. Girdles and bras can contain rubber. Rubber panties may irritate the skin of babies. Rubber gloves can irritate the hands. Rubber shoes can cause foot rash.

Thousands upon thousands of people color their hair and will continue to do so without difficulty. But some people who dye their hair will develop allergic hypersensitivity to an ingredient found in permanent hair dyes. These are usually called tints. If tints cause rash sometimes a semipermanent dye or vegetable rinse will serve almost as well.

The person who develops allergic contact dermatitis can make life much happier if he learns to avoid the substance that causes the reaction and all materials that cross-react with it. There are safe substitute products for virtually everything.



July, 1980
Frank Chappell
Science News Editor
AMA

BOLETIN

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(USPS-060000)

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Fundado en 1903

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VACUNACION: PRINCIPIOS Y PRACTICA 1980
REVISION Y CONCEPTOS — PARTE I
Desarrollo histórico, Efectos Secundarios Difteria, Tétanos
y Tos Ferina, Poliomieltis y Sarampión

Carlos H. Ramírez Ronda, MD, FACP, Ramón H. Bermúdez, MD, FACP,
Manuel J. Pérez Pabón, MSIV y Rafael A. Quiñones-Soto, MD

Resumen: La vacunación ha sido tradicionalmente reconocida como un área de interés pediátrico. En la práctica actual de la medicina, la vacunación se aplica a todas las edades. En esta sección se presenta a grandes rasgos el desarrollo histórico de la vacunación con énfasis en los eventos históricos significativos, inmunización pasiva, inmunización activa, vacunas bacterianas, los toxides y vacunas virales. Se presenta una breve relación de los efectos secundarios que se asocian a la vacunación y se trata de diferenciar accidentes asociados a vacunas de efectos secundarios. Se discuten y repasan los efectos neurológicos de las vacunas.

Se presenta el uso, indicaciones y contraindicaciones de las vacunas de difteria, tétanos y tosferina. Se enfatiza el uso de toxide y de inmunoglobulina humana antitetánica en el paciente adulto. Se enfatiza la importancia de la inmunización primaria, en cualquier

edad.

Se discute la vacunación en contra de poliomieltis y se presentan alternativas para la vacunación de adultos previamente no inmunizados. Se discute el riesgo del adulto no inmunizado al exponerse en su casa a un niño que recibió la vacuna oral trivalente de polio. Se discute la relación de polio en casos importados y en pacientes inmunocomprometidos. Se presenta y se discute la vacuna de sarampión, su uso y efectos secundarios. Se enfatiza la importancia de conocer el tipo de vacuna que recibieron cuando niños, los hoy adultos jóvenes. Se presenta la relación entre esta vacuna y el sarampión atípico.

Summary: The use of vaccines has been traditionally recognized as an area of pediatric interest, today the practice of medicine requires knowledge of immunization in all age groups. In this section we present the historical development of immunization with special interest on the historical events of significance, passive immunization, active immunization, bacterial vaccines, development of toxoids and viral vaccines. The side effects associated with the use of vaccines is presented and we try to differentiate accidents with vaccines from side effects. There is special

De los Departamentos de Investigación y Medicina, Hospital de Veteranos y Escuela de Medicina, Universidad de Puerto Rico, Laboratorio de Investigación en Enfermedades Infecciosas del Hospital de Veteranos y Programa de Entrenamiento en Enfermedades Infecciosas de la Escuela de Medicina, UPR y Hospitales Afiliados.

Favor pedir reimpresos a: Carlos H. Ramírez Ronda, MD, FACP, VA Med. & Reg. Office Center, Inf. Dis. Research Lab. (151), GPO Box 4867, San Juan, Puerto Rico 00936.

emphasis on the neurologic side effects of vaccines.

The use, indications and contraindications of the diphtheria, tetanus and pertussis vaccines is presented. The use in the adult patient of tetanus toxoid and tetanus immune human globulin is presented. There is emphasis on primary immunization in any and every age group.

The polio vaccine, its use and route is discussed. The immunization of adults not previously immunized and the risk of development of polio in such a patient is discussed. The relationship of polio in adults with exposure to children recently immunized with oral polio is presented. There is a presentation of imported polio as well as polio in the immunocompromised host.

Measles vaccines, its use and types and side effects is presented. The importance to know the type of vaccine received when our young adults were children is discussed. The relationship of vaccination to atypical measles is presented.

Introducción

Hasta hace poco tiempo la vacunación se reconocía como un área exclusiva de los pediatras, pero cambios en los patrones de enfermedad, el desarrollo de nuevas vacunas y el aumento de viajes al extranjero, han hecho que el médico internista y el médico de familia necesiten rutinariamente de un conocimiento vasto sobre las inmunizaciones y su uso en la práctica de la medicina en general. La historia (1) de la vacunación comienza con Edward Jenner y sus investigaciones documentando la prevención de la viruela por inoculación del virus de la viruela vacuna. La efectividad de esta vacuna y sus modificaciones

se reflejan en que actualmente la viruela se ha extinguido globalmente. Cuando Jenner publicó su trabajo, la viruela era causante del 10 al 20 por ciento de todas las muertes que ocurrían en Gran Bretaña. No se desarrollaron más vacunas hasta que surgió la era dorada de la bacteriología en 1876 cuando en un término de 10 años se hicieron grandes descubrimientos microbiológicos. Existía una gran competencia entre dos escuelas: la Escuela Berlinesa, dirigida por el Dr. Roberto Koch, y la Escuela Parisiense, encabezada por el Dr. Luis Pasteur. La segunda vacuna mundial fue desarrollada en contra de la cólera aviana, hallazgo hecho por casualidad cuando se demostró que si se inoculaban cultivos viejos de estos microorganismos, se protegía al animal de una infección subsiguiente. Posteriormente, en el 1865, Pasteur desarrolló la vacuna de rabia mediante el uso de organismos atenuados obtenidos al secar la preparación, lo cual llevó al tratamiento profiláctico de rabia. A pesar de que los experimentos de Pasteur poseían fundamentos científicos, él no tenía un concepto correcto de lo que era inmunidad, creyendo que los agentes atenuados estaban consumiendo sustancias nutricionales esenciales las cuales subsiguientemente no estarían presentes para que los microorganismos virulentos las utilizaran. Fueron Behring, Ehrlich y Metchnikoff quienes formularon los postulados básicos de inmunidad.

Las vacunas bacterianas más efectivas fueron dirigidas en contra de toxinas como las de difteria y tétanos. Inicialmente, la vacuna de difteria consistía en una mezcla de toxina y antitoxina. Como resultado de esto, en muchas ocasiones la toxina no estaba contrabalanceada por una cantidad correspondiente de antitoxina y ocurrieron algunos accidentes serios. Al modificar las toxinas con formalina se prepararon los toxoides, siendo éstos los componentes básicos en las vacunas

actuales. La inmunogenicidad de los toxoides se incrementó utilizando precipitados de aluminio. Otras vacunas bacterianas fueron desarrolladas en contra de tifoidea, paratifoidea, cólera y plaga, y consistían de preparaciones crudas de microorganismos enteros muertos. Estas permanecen siendo inmunógenos pobres cuya ineficacia no fue constatada hasta los años 1960 mediante estudios controlados. Las facetas más importantes en el desarrollo de las vacunas bacterianas modernas son: el aislamiento y la caracterización y purificación de los antígenos específicos responsables de la virulencia e inmunidad. Ejemplos de estos antígenos son: la toxina elaborada por *Cholera vibrio* y el polisacárido capsular de los neumococos y meningococos A y C.

Al descubrirse que algunos virus podían ser cultivados en huevos embrionados de pollo y posteriormente en cultivos de tejidos, se comenzó el desarrollo de las vacunas virales. Las más efectivas consistían de virus vivos atenuados los cuales aparentemente proveen una inmunidad a largo plazo con una simple inoculación, documentándose muy pocos efectos secundarios. Existen vacunas de virus inactivados para influenza, rabia y poliomiелitis.

Al reconocerse que aquellas vacunas en contra de sarampión y el virus respiratorio sincitial eran capaces de producir un cuadro clínico atípico, el cual en numerosas ocasiones era aún más severo que el de la enfermedad natural, el desarrollo de estas vacunas sufrió retrasos.

Paradójicamente, los avances en el desarrollo de vacunas muchas veces resultan en retrocesos, ejemplo de esto es el hecho de que mientras más purificada sea la vacuna, ésta puede que resulte ser menos inmunogénica. Se considera factible en un futuro cercano el desarrollo de nuevas vacunas en contra de agentes como *Hemophilus influen-*

zae, el estreptococo grupo B y *Neisseria gonorrhoeae*. Los factores que pueden limitar el uso de éstos incluyen: El demostrar sin lugar a dudas de que la enfermedad que se va a prevenir constituye un problema de salud pública y en segundo lugar, la aceptación de la nueva vacuna como medida de prevención primaria.

Accidentes Asociados con Inmunizaciones

Desde que se comenzó a inmunizar han ocurrido una serie de accidentes que se han asociado a factores en la producción o en la administración de las vacunas (2). En cuanto a los factores en la producción, el defecto puede estar (1) en el hecho de que el virus o toxina en la vacuna esté inactivado incompletamente o no está inactivado; (2) que exista una toxina foránea en el material; (3) que se haya utilizado el medio de cultivo no adecuado o; (4) que haya ocurrido contaminación bacteriana o viral. La administración inadecuada de la vacuna puede ocurrir porque se utilice un aparato no estéril o que haya ocurrido contaminación bacteriana por la persona que administra la vacuna. Los accidentes usualmente ocurren durante las primeras fases de la manufactura, siendo mucho más comunes durante la primera parte de este siglo cuando las vacunas eran fabricadas por pequeños laboratorios los cuales tenían un control de calidad pobre. Los accidentes deben de considerarse separadamente de las complicaciones que pueden ocurrir después de una inmunización. La investigación de las causas de los accidentes ha resultado en mejoras significativas, ya que estos accidentes identificaron las etapas en la manufactura donde la propensidad a cometer errores era más alta.

El Incidente Cutter (3)

Después que los doctores Enders, Wel-

lers y Robins cultivaron el virus de poliomielitis en cultivos de tejidos, Salk introdujo una vacuna que contenía los tres virus de poliomielitis inactivados con formalina. El estudio de efectividad de Francis, demostró la efectividad protectora de esta vacuna. Seis diferentes fabricantes farmacéuticos fueron licenciados para producir la vacuna, la cual fue administrada aproximadamente a cinco millones de personas comenzando en abril del 1955. El 26 de abril, seis casos de poliomielitis fueron identificados en niños que habían recibido la vacuna manufacturada por los laboratorios Cutter. Estos casos habían tenido un período de incubación corto (9 días). La parte del cuerpo donde la parálisis se manifestó inicialmente fue usualmente el brazo en donde se había administrado la vacuna. Esto es característico cuando ocurre poliomielitis después de una inoculación. Subsiguientemente ocurrieron casos en contactos familiares y contactos en la comunidad. Los casos originales fueron examinados para la excreción fecal del virus y el 80 por ciento de los niños inyectados que habían desarrollado parálisis tenían el virus de poliomielitis tipo 1 en sus heces. El virus fue también recuperado de la vacuna. Tan pronto los primeros casos se identificaron, todos los lotes de la vacuna Cutter se decomisaron. Durante la epidemia ocurrieron 260 casos de poliomielitis en todo el país, 10 de los cuales murieron. Noventa y cuatro casos en personas vacunadas, 126 en contactos familiares y 40 en contactos de la comunidad. Se demostró que en algunas de las vacunas el virus no había sido inactivado por formalina. El incidente Cutter (3) llevó a reconocer la necesidad de tener controles de calidad adecuados en la preparación de vacunas.

Las Complicaciones de Vacunación

Sir Graham S. Wilson en "The Hazards

of Immunization" dice, "there can't be no insurance without a premium" (2). Cada vacuna es un producto biológico con toxicidad inherente la cual debe de ser comparada con su valor protector en contra de la enfermedad que estamos tratando de evitar. Las complicaciones puede ser locales y relacionadas a productos como las endotoxinas, contaminación de las vacunas con bacilos gram-negativos muertos, etc. El fenómeno de Arthus está implicado en la patogénesis de alguna de las reacciones locales. Abscesos estériles pueden ocurrir después de la inoculación. En parte, la severidad de la reacción local puede ser disminuida mediante la purificación del producto. La vacunación en contra de tifoidea puede estar acompañada de efectos secundarios, ya que el producto que produce la reacción, endotoxina, es una componente inherente de la vacuna. Mediante el proceso de retrocentrifugación de zona se ha podido purificar la vacuna de influenza, aislando así los productos contaminantes provenientes del huevo embrionado. Reacciones secundarias tanto locales como sistémicas puede estar relacionadas a la presencia del virus. Si el virus se fragmenta químicamente en unidades y subunidades, los efectos secundarios disminuyen al igual que la efectividad inmunogénica de la vacuna en específico cuando se administra a personas que no han tenido una experiencia inmunológica previa con otros de los virus de influenza. Al mantener el virus intacto, la inmunogenicidad del mismo no disminuye. Las reacciones febriles, el malestar y los dolores musculares después de una inmunización son causados por mecanismos locales. Reacciones alérgicas severas pueden complicar la vacunación hasta incluir algunos, si no todas las manifestaciones clásicas de la anafilaxis. Como muchas de las vacunas se producen en huevos embrionados de gallinas, se le debe advertir a las personas que son alérgicas a los productos de huevos que no

deben ser inmunizadas a menos que se tomen precauciones específicas.

Los efectos secundarios y las reacciones que pueden ocurrir después de la vacuna de viruela son severos, y llevaron a que se reconsiderasen los criterios de su uso aún en aquellos lugares donde la viruela no era endémica. Estos efectos secundarios precluyen el uso de la vacuna para ningún otro propósito que no sea para el que originalmente se diseñó. El uso de la vacuna de viruela para tratar de alterar el curso de infecciones herpéticas recurrentes o para curar verrugas no tiene documentación científica alguna y puede ser acompañada por consecuencias graves. Las reacciones de piel que siguen a una vacunación de viruela han sido estudiadas minuciosamente y consisten de los efectos que se deben a la replicación del virus y a las manifestaciones alérgicas. Como el virus se está replicando, puede ser transmitido a personas que han estado en contacto íntimo con aquellos que reciben la vacuna. El virus puede diseminarse y afectar otras áreas de la piel resultando en cuadro de lo que se llama *eczema vaccinatum*. En algunos pacientes con defectos inmunológicos, el virus se disemina del foco primario de vacunación a otros lugares. Esta reacción, conocida como *vaccinia necrosum* puede ser fatal a menos que se utilice la inmunoglobulina específica en contra de *vaccinia* y las *tiosemizcarbazonas*. Las reacciones alérgicas consisten de urticaria, eritema tóxico, púrpura anafilactoide y eritema multiforme generalizada.

En su tratado clásico, Miller y Stanton (4), revisaron extensamente las complicaciones neurológicas que pueden surgir después de una vacunación. Estas reacciones como resultado de la administración de cualquier agente inmunogénico aparentemente son más comunes después de algunas vacunas que

otras. La encefalitis que sigue a la vacuna de viruela puede ser severa, y en algunos países ocurre con tanta frecuencia como en 19 de cada 100,000 personas de edad militar que reciben la vacunación primaria. La vacuna Semple en contra de la rabia también se ha destacado por su tendencia a causar manifestaciones neurológicas significativas. A pesar de que ha ocurrido una disminución substancial con el uso de vacunas desarrolladas en embriones de patos, las mismas reacciones pueden ocurrir con este producto. Se ha reconocido un síndrome neurológico post inmunización que incluyen encefalitis, encefalopatía, encefalomielitis diseminada, mielitis transversa y neuropatía periférica de origen agudo, ya sea localizado o generalizado (4). La forma localizada de una neuropatía periférica aguda usualmente tiende a involucrar el plexo braquial. Al ocurrir una reacción generalizada, usualmente se presenta como el Síndrome de Guillain-Barré.

Algunas vacunas, como es el toxoide de tétano, son rara vez asociadas con cuadros clínicos o efectos neurológicos secundarios. Otras, nunca se habían asociado a reacciones neurológicas, como en el caso de la vacuna de influenza, hasta que un gran número de vacunas fueron administradas durante un corto período de tiempo. Durante este tiempo se dio seguimiento a cada una de las personas que recibían la vacuna; este esfuerzo y seguimiento de cerca llevó a descubrir la asociación de la vacuna de influenza con el síndrome de Guillain Barré (5, 6). La ocurrencia de diferentes tipos de síndromes neurológicos después de un período latente y la similitud de éstos con los procesos patológicos que pueden ocurrir después de la administración de suero equino, refuerzan la importancia de los mecanismos inmunológicos que describen Miller y Stanton. "The Common Factor in the Pathogenesis of these Cases comprising encephalitis, myelitis,

Landry, Guillain-Barré, radicular, polyneuritic, and mononeuritic syndromes, is anaphylactic hypersensitivity, and that a similar mechanism may be involved in many of the identical neurological illnesses which may alter independently of preceding inoculation" (4). La mayoría de las vacunas actuales contienen advertencias del peligro potencial de reacciones neurológicas que pueden evidenciarse después de la administración parenteral de cualquier sustancia biológica (7, 8, 9, 10).

Difteria, Tétanos y Tos Ferina

La vacuna original de difteria fue una mezcla de toxina y antitoxina seguida por un precipitado de las mismas. En los años 1920 se descubrió que el tratamiento de la toxina con formaldehído resultaba en la pérdida de su toxicidad pero no de su antigenicidad. Las vacunas de toxoide de tétano también se prepararon mediante el mismo proceso de inactivación. En el presente existen vacunas individuales para cada uno de los toxoides pero la mayoría de las inmunizaciones se llevan a cabo usando las vacunas combinadas de difteria, tétanos y tos ferina (DPT) o la combinación de tétanos y la dosis de adulto de difteria (Td). Después del advenimiento y uso en grande escala de estas vacunas, la incidencia de cada una de estas enfermedades ha disminuído marcadamente. A su vez, junto con la disminución de los casos de difteria, la prevalencia de la colonización en la nasofaringe con *Corynebacterium diphtheriae* también disminuyó. Debe anotarse que la vacunación con los toxoides de diphtheria no afecta la tasa de portadores para este organismo (11, 12). A pesar de que la incidencia de tos ferina fue igualmente afectada, la ocurrencia reciente de brotes locales de tos ferina en algunas áreas

de Estados Unidos indican que aún tenemos problemas con este patógeno. La distribución de las esporas de tétanos en el terreno y la contaminación presunta de heridas con *Clostridium tetani* no ha cambiado desde la introducción de la vacuna toxoide de tétano. La vacuna no previene en esencia la infección, solamente previene la enfermedad.

La epidemia de difteria en Austin, Texas y subsiguientemente en San Antonio en los años 68 y 70 demuestran que este microorganismo puede causar problemas en las áreas modernas urbanas de Estados Unidos y particularmente en Puerto Rico (13, 14). En San Antonio (11) en 1970 ocurrieron casos a través de todo el año con picos de prevalencia durante la parte final del verano. Predominaron los casos en las personas no vacunadas en el área central de la ciudad. Los niños entre las edades de 1 a 4 y 5 a 9 años fueron afectados particularmente. La razón entre casos y fatalidad fue baja, 1.8 por ciento, en contraste a la cifra nacional en donde la razón de casos a fatalidad era aproximadamente 10 por ciento. Es probable que la tasa baja de mortalidad en San Antonio se debió a que se reconoció temprano la situación epidémica y que esta se controló. La epidemia fue controlada mediante el tratamiento presuntivo de los portadores con antibióticos, campañas en la población sobre la necesidad de vacunación y el movimiento de equipos de vacunación a las áreas afectadas de la ciudad.

El problema de tos ferina en los E.U.A. puede que recurra, ya que la inmunidad existente en la población adulta ha ido disminuyendo. Esta inmunidad fue inducida cuando los adultos de hoy eran niños, unido al hecho de que la inmunización pre-escolar de ciertos grupos poblacionales no ha sido efectiva (15-20). Brotes recientes en donde han estado involucrados casos de adultos han sido res-

ponsables por diseminar los microorganismos a otros adultos y a pacientes pediátricos. La enfermedad en adultos fue prolongada y severa, con un curso clínico que duró a veces hasta 10 semanas, acompañada por paroxismos de tos seguida por vómitos y asociadas con la sensación de perder la respiración.

En Puerto Rico hay alrededor de 15 a 20 casos reportados de tétanos al año (21). La mayor parte de éstos ocurren en personas de 50 años de edad o más. La herida que inicia el proceso usualmente es una de carácter trivial y los pacientes usualmente no han recibido vacunación o puede ser que una sola dosis de toxoide en el pasado.

Los casos de tétanos en el neonato han disminuído significativamente en Puerto Rico y los adictos no constituyen un problema todavía. El problema con los tétanos en la actualidad se solucionaría si inmunizásemos primariamente a nuestros adultos envejecientes. Aquellos que nunca han estado vacunados deben de recibir tres dosis de la vacuna. Aquellos vacunados debemos sostener la inmunidad mediante refuerzos con dosis de toxoide cada 10 años (21, 22, 23, 24). Un estudio demostró que en Puerto Rico el 50 por ciento de las personas de 50 años de edad o más no tenían protección en contra de tétanos (25, 26) (Véase Tabla I).

Con las preparaciones modernas las reacciones a la vacuna de DPT o Td son raras y cuando ocurren se deben principalmente al componente de tos ferina. La presentación clínica usual de una reacción severa después de una vacuna de tos ferina (18) se asocian a la ocurrencia de encefalopatía, generalmente ocurriendo en o dentro de las primeras 24 horas de recibir la vacuna, pero puede demorarse hasta dos o tres días. La reacción se caracteriza por episodios incontrolados e inexplicados de gritos o convulsiones. Un síndrome parecido a una encefalitis, con pérdida de

conciencia, convulsiones repetidas, complicaciones neurológicas persistentes o prolongadas y ocasionalmente muerte ha sido descrito pero muy infrecuentemente. El componente de difteria de la vacuna de adultos Td se reduce comparado al de la dosis pediátrica por un factor de 1:10. Esta disminución antigénica en la vacuna Td previene que en el adulto ocurran efectos secundarios significativos relacionados a la reacción de hipersensitividad tardía a los componentes de la vacuna. La administración demasiado frecuente del toxoide de tétano resulta en una incidencia alta de reacciones alérgicas (27).

No se puede predecir si después de ocurrir la enfermedad de difteria o tétano ocurre inmunidad (12, 22). Después de la enfermedad el paciente debe inmunizarse primariamente (Véase Tabla I). Si esta inmunización no se lleva a cabo, el médico puede ser responsabilizado si el paciente desarrollase nuevamente la condición. La inmunización en el adulto debe de renovarse con dosis de vacuna Td cada 10 años. La vacuna precipitada con aluminio se prefiere para inmunizaciones de rutina, mientras que el toxoide líquido puede utilizarse cuando se quiera un aumento rápido en anticuerpos (27, 28). En la Tabla II demostramos el regimen de vacunación de tétano que debe de utilizarse cuando el paciente tiene una herida y está basado en el estado de inmunización y en el tipo de herida (21). En nuestra sociedad la difteria y el tétanos no debían de ocurrir jamás. El hecho de que ocurren indica que hemos fracasado en proveer a la población con unos inmunógenos que son efectivos y protectivos.

Poliomielitis

El evento histórico de mayor importancia en el control de la poliomielitis fue el

TABLA I
Inmunización Básica
Para Obtener Protección Adecuada Contra el Tétano

<i>Primera Dosis</i>	<i>0.5 ml toxoide de tétano</i>
<i>Segunda Dosis</i>	<i>0.5 ml toxoide de tétano 4 a 6 semanas después de la primera dosis</i>
<i>Tercera Dosis</i>	<i>0.5 ml toxoide de tétano 6 a 12 meses después de la segunda dosis</i>

TABLA II

Recomendaciones del Comité Asesor en Prácticas de Inmunización de los Estados Unidos para la Prevención del Tétano en Pacientes con Heridas

<i>Historial de Inmunización contra el tétano</i>	<i>Heridas Limpias, Menores</i>		<i>Heridas Mayores</i>	
<i>Número de Dosis</i>	<i>Toxoide</i>	<i>Globulina Humana</i>	<i>Toxoide</i>	<i>Globulina Humana</i>
<i>Desconocido</i>	<i>Sí</i>	<i>No</i>	<i>Sí</i>	<i>Sí₄</i>
<i>0-1</i>	<i>Sí</i>	<i>No</i>	<i>Sí</i>	<i>Sí₄</i>
<i>2</i>	<i>Sí</i>	<i>No</i>	<i>Sí</i>	<i>No₂</i>
<i>3 o más</i>	<i>No₁</i>	<i>No</i>	<i>No₃</i>	<i>No₁</i>

1 A menos que hayan pasado más de 10 años desde la última dosis

2 A menos que tenga más de 24 horas.

3 A menos que hayan pasado más de 5 años desde la última dosis.

4 250 unidades.

cultivo del virus en cultivos de tejidos por Enders, Weller y Robins lo cual les valió el premio Nobel. Posteriormente, Salk desarrolló una vacuna de virus inactivada en formaldehído utilizando tres cepas de virus de poliomiélitis. Koprowsky, Koch y Sabin trabajaron para producir una vacuna de virus atenuados vivos con la cepa Sabin del virus, la cual fue eventualmente aceptada (29). La vacuna de poliomiélitis Salk inactivada fue probada en el 1954, en lo que se conoce como la prueba de campo de Francis. Se reconoció más tarde que la inactivación con formaldehído era insuficiente para destruir uno de los contaminantes comunes del cultivo de tejidos de riñón de primates. Este virus es el SV40, un papovirus, y se ha demostrado que tiene potencial oncogénico. Afortunadamente, en los estudios subsiguientes de las personas que recibieron el virus SV-40 inadvertidamente, no se ha encontrado evidencia de que este virus haya inducido tumores, a pesar de que se ha demostrado por métodos serológicos que ocurrió infección. En los Estados Unidos de Norteamérica y muchos otros países con la exclusión de Suecia y Finlandia la vacuna Salk fue reemplazada por la vacuna Sabin. La vacuna Sabin es la vacuna oral de poliomiélitis monovalente y trivalente. El incidence Cutter enfatizó la necesidad para el rastreo de las complicaciones después que se introduce cualquier vacuna nueva. Estas técnicas de rastreo eventualmente culminaron en el descubrimiento de las tasas de complicaciones definidas tanto de la vacuna oral como de cualquier otra vacuna. Por ejemplo, el rastreo de las personas que recibieron la vacuna oral de polio demostró la asociación entre la administración de la vacuna y poliomiélitis. Estos casos pueden clasificarse en tres grupos: las personas que reciben la vacuna, las personas que viven en el mismo hogar de

las personas que reciben las vacunas y el tercer lugar, los contactos no familiares de las personas que recibieron la vacuna (30, 31, 32). El informe original documentando la ocurrencia de casos de poliomiélitis asociados a la vacuna indican que éstos son poco frecuentes. Los patrones epidemiológicos son diferentes en estos casos cuando se comparan con los que ocurren con una infección natural. La mayor parte de los casos puede relacionarse temporalmente con la administración de la vacuna oral monovalente del tipo III (30). En el estudio de 1964, 46/57 casos ocurrieron en varones y 25/46 de los casos en varones en las edades de 15 a 39 años. Se estimó también que después de administrar oralmente la vacuna tipo I, ocurrían 0.17 casos por millón de dosis de vacuna. El comité especial nombrado por el Servicio de Salud Pública recomendó un cambio en el orden de la administración de la vacuna oral monovalente a los infantes; esta fue el tipo II seguido por tipo I y seguido por tipo III, recomendando que la inmunización rutinaria de adultos no se haga en aquellas personas que no habían estado inmunizadas previamente (33).

El control de poliomiélitis depende de la inmunización rutinaria de infantes y niños. Los adultos deben ser inmunizados primariamente solamente si están en un alto riesgo o si van a viajar a áreas endémicas de poliomiélitis. En los años subsiguientes al informe, la vacuna oral monovalente en contra de polio fue reemplazada por la vacuna oral trivalente de polio. La cepa del virus tipo III en la vacuna ha sido modificada y atenuada aún más. En los Estados Unidos de Norteamérica la vacuna inactivada de polio no se encuentra para uso en la mayor parte de los estados.

Como resultado de los cambios en el

uso de la vacuna, los patrones epidemiológicos de la poliomielitis han cambiado de la siguiente forma: (1) A pesar de que las situaciones epidémicas son muy poco probables, una epidemia del tipo I poliomielitis ocurrió en 1970 en Tejas cerca de la frontera mejicana causando 22 casos. En 1972 una epidemia ocurrió en una escuela de una secta religiosa en Connecticut con 8 casos. Estos dos incidentes demostraron un número significativo de niños de edad pre-escolar sin vacunación. El potencial de una epidemia general en los Estados Unidos de Norteamérica existe, ya que los programas de inmunización no han sido muy efectivos en los niños de edad pre-escolar; (2) *Los casos importados*. En el intervalo de 1969 a 1977, ocurrieron 15 casos importados de poliomielitis en los Estados Unidos. La mayor parte de estos provinieron de las áreas cercanas a la frontera, indicando el riesgo de la importación de personas sin vacunación. (3) *Casos endémicos no asociados a vacunación*. Treinta y dos casos ocurrieron en los Estados Unidos de Norteamérica fuera de situaciones epidémicas en el intervalo del 1969 al 1976. Algunos de éstos pueden haber estado relacionados a virus de la vacuna. Desde el informe de 1964 ha ocurrido un cambio en la razón de los casos de poliomielitis que ocurren entre las personas que reciben la vacuna y entre las personas expuestas a los recipientes de la vacuna. En el momento la razón es de 10:34 con la mayor parte de los casos relacionados a vacuna ocurriendo en contacto de los pacientes que recibieron esta vacuna. Evidentemente, la vacuna oral trivalente en donde se ingiere un tipo tres más atenuado y el énfasis en la inmunización de infantes y niños ha resultado en un cambio de los casos asociados a vacuna a los contactos de los recipientes de la vacuna, particularmente aquellos en las edades de 20 a 39 años (34). Prácticamente, esto resulta en un aumento en el riesgo a las personas no inmunizadas, particularmente padres de niños

jóvenes que recibirán inmunización rutinaria y principalmente mandatoria al entrar a la escuela. Existe un grupo de personas que son en la actualidad adultos jóvenes los cuales no han sido inmunizados en contra de poliomielitis. Como la vacuna inactivada tipo Salk no se encuentra en uso, el problema principal se relaciona al manejo de estos adultos jóvenes no inmunizados, principalmente padres de niños de edad pre-escolar. Esto es particularmente pertinente ya que desde 1977 la razón de casos de polio no vacunados a vacunados fue de 14 a 4. Se recomienda como parte de la estrategia nacional en contra de poliomielitis que se tenga a mano la vacuna inactivada tipo Salk lista para utilizarse en situaciones limitadas con el fin de iniciar algún tipo de inmunidad; la inmunización completa debe efectuarse posteriormente con la vacuna oral (33). (5) *Casos de poliomielitis en pacientes con inmunodeficiencias*. Durante el intervalo de los años 1969 al 1976 ocurrieron 11 casos en este grupo de personas incluyendo 5 muertes. La mayor parte de estas personas estuvieron expuestas a vacuna oral de poliomielitis ya sea como recipiente o como contacto de un recipiente. El intervalo entre la exposición al virus de la vacuna y el comienzo de la enfermedad fue prolongado en varios de los casos, surgiendo que la infección era con el tipo de virus salvaje o que una respuesta atenuada había ocurrido. Se ha informado que en personas con deficiencias inmunes, el virus de la vacuna puede producir cambios subagudos y crónicos y que éste puede ser aislado del sistema nervioso central meses después de que ha comenzado la enfermedad.

Ya que el virus de poliomielitis es uno cuyos tipos pueden interferir con el crecimiento de otros tipos en el tracto gastrointestinal humano, es necesario administrar tres dosis de la vacuna oral polivalente para asegurar inmunidad. En los infantes la in-

munización se comienza de 6 a 12 semanas de edad con una segunda dosis de vacuna administrada de 6 a 8 semanas más tarde. Se administra una tercera dosis de vacuna aproximadamente al año de edad y una dosis de refuerzo al comenzar en la escuela. Dosis adicionales no son necesarias a menos que las personas estén entrando en situaciones de alto riesgo y en esta situación, se administra una dosis sencilla de vacuna oral de poliomielitis (32). Las vacunas orales de poliomielitis se producen en cultivos de tejidos de monos. Una vacuna se ha producido en células del tipo WI-38 y se ha utilizado en el extranjero. El sustrato celular está bien definido para las células WI-38. Basándonos en lo anteriormente expuesto y en que el número de primates no está limitado, esta vacuna eventualmente reemplazará a la presente en el mercado.

Sarampión

La rubeolla o sarampión común constituye una causa significativa de morbilidad en la niñez. Puede producir una pulmonía viral conocida por pulmonía de células gigantes. Los pacientes están predispuestos a infección bacteriana en el pulmón y del oído medio. La encefalitis subsiguiente al sarampión ocurre en uno de mil casos, tiene una tasa alta de casos fatales (40 por ciento) y los pacientes que sobreviven tienen secuelas significativas. Después de un período prolongado de latencia, el virus de sarampión puede causar infección del cerebro y manifestarse como panencefalitis esclerosante subaguda la cual es infrecuente pero uniformemente fatal. La tasa de panencefalitis esclerosante subaguda subsiguiente al sarampión ha sido estimada en 5.2-9.7 casos por millón de casos de sarampión (35).

Enders y Peebles aislaron el virus de sarampión en cultivos de tejidos en 1953. La

primera vacuna de virus atenuado en contra del sarampión, la vacuna con la cepa Edmonson B, fue autorizada para usarse en los Estados Unidos diez años más tarde. En 1960-61 una vacuna con un virus muerto fue introducida y usada durante aproximadamente dos años antes de que se removiese del mercado. La vacuna original con virus vivo causó un gran número de reacciones secundarias necesitándose una inyección de gamma globulina la cual tenía que ser administrada concurrentemente para suprimir la severidad de éstos. Posteriormente, cepas más atenuadas del virus se desarrollaron por lo cual la administración de gamma globulina no era necesaria. Durante las primeras fases en la administración de esta vacuna no se derivó datos para determinar cual sería la edad óptima para administrar la vacuna. Idealmente, el niño debe de estar libre de los anticuerpos transmitidos por la vía materna y debe tener suficiente madurez inmunológica para que la respuesta sea duradera. La vacuna liofilizada se administra después de reconstituirse con agua estéril; la efectividad como agente inmunizante se limita a unas 8 horas, si se mantiene a cuatro grados centígrados. Es probable que al comienzo de la vacunación con este producto el mismo fuese administrado de forma inactivada a un por ciento no determinado de la población pediátrica. Para inducir inmunidad adecuada se necesitó varias inyecciones de la vacuna muerta.

La vacuna con virus vivo atenuado podía administrarse en una dosis sencilla. Cuando se le confirió licencia a la vacuna, las primeras personas en inmunizarse fueron los niños pequeños de las clases socioeconómicas media y alta. El sarampión disminuyó en incidencia, pero persistió en las ciudades centrales con la mayoría de los casos ocurriendo en niños preescolares. Con la baja en la incidencia de sarampión lograda a través de la inmunización

se logró que muchos niños escaparan del sarampión natural, pero estos mismos niños muchas veces fueron considerados muy viejos para ser inmunizados, dejando una población sin inmunidad. El sarampión resurgió en el año 1970-71. En estas epidemias las tasas de ataques en niños jóvenes tendían a ser mayores en las áreas de nivel socioeconómico más bajo que en los niños de nivel socioeconómico más alto. Esta situación reflejó el hecho de que había ocurrido transmisión de sarampión en los vecindarios socioeconómicamente bajos pero que la misma no había ocurrido en los vecindarios de niveles socioeconómicamente más altos. Cuando surgió la epidemia, la circulación del virus de sarampión se extendió a aquellos barrios donde el virus no había circulado normalmente y los niños de edades mayores, los cuales no habían sido inmunizados o habían sido inmunizados con la vacuna de virus muerto o que en el momento de epidemias previas eran muy jóvenes para desarrollar sarampión natural, desarrollaron entonces la enfermedad. El resurgimiento del sarampión de 1970 al 71 y los eventos subsiguientes apuntan lo siguiente (36, 37): (1) La vacuna de sarampión muerta fue inadecuada. Las personas que recibieron esta vacuna y que sufrieron más tarde la experiencia del sarampión natural desarrollaron sarampión atípico. Por lo tanto, estos niños tenían que ser inmunizados nuevamente con las vacunas modernas; (2) Los niños que recibieron gamma globulina con la cepa Edmonson B de la vacuna no pueden darse por protegidos y deben ser reinmunizados; (3) los niños que se vacunaron en una forma inadecuada deben de ser reinmunizados; (4) los niños que fueron fracasos de la vacuna se relacionaron mayormente al hecho de que el virus de la vacuna podría estar inactivado.

Conociendo los hechos de que algunos

niños particularmente durante los primeros días de la vacuna no fueron inmunizados correctamente, la vacuna probó así mismo ser efectiva a un nivel del 95 por ciento. Estudios subsiguientes en niños inmunizados adecuadamente revelan la persistencia de anticuerpos la cual es similar a la de los anticuerpos adquiridos naturalmente, pero a un nivel más bajo. Sin embargo, estos son protectivos (38).

Los eventos según han sido presentados arriba crean una situación especial epidemiológicamente con respecto a sarampión; niños preescolares, particularmente en las ciudades centrales continúan estando inadecuadamente protegidos en contra de la enfermedad. Al entrar a la escuela estos mejoran su estado de inmunización debido a las prácticas mandatorias. Muchas veces, niños de los niveles socioeconómicos más bajos y de áreas rurales pueden estar en la actualidad inadecuadamente protegidos en contra de sarampión y como una consecuencia de esto, en los próximos años veremos sarampión en el adulto joven como un problema que va en aumento (39-44). Esto se ha comenzado a manifestar por brotes de sarampión en escuelas secundarias, colegios y en poblaciones de reclutas. El problema se agrava mediante el hecho de que vivimos en una sociedad móvil y la manera exacta por la cual un niño fue inmunizado no está accesible para ser revisado. Otro hecho es que las personas puedan creer que ya tuvieron sarampión, cuando en la actualidad lo que sufrieron fue una erupción eritematosa. Los médicos jóvenes al no haber estado en contacto frecuentemente con el sarampión durante su entrenamiento carecen de destreza en el diagnóstico de estos casos. El sarampión en el adulto joven promete ser un problema que va en aumento y al momento presente tenemos evidencia insuficiente para predecir cual

será su curso clínico.

Los niños vacunados con la vacuna del virus muerto, una vez son re-expuestos a la vacuna de virus vivo o al virus natural de sarampión pueden sufrir reacciones locales severas en el lugar de inoculación de la vacuna o pueden desarrollar sarampión atípico (35, 47). El sarampión atípico consiste de una erupción macopapular con componentes vesiculares y purpúricos, comenzando en las extremidades y dirigiéndose centralmente concomitante con consolidación pulmonar y efusión pleural acompañada por una reacción eosinofílica. Los títulos de anticuerpos virales aumentan y disminuyen eventualmente como debería de esperarse, pero el virus no puede recobrase del tracto respiratorio. Las áreas de consolidación pulmonar no son de etiología bacteriana. La patogénesis de estas manifestaciones no están claras más se sabe que la vacuna de sarampión con virus muerto únicamente induce anticuerpos en contra de la hemaglutina del virus y no en contra de la hemolisina. La patogénesis de este desorden probablemente incluye algún componente de la respuesta de hipersensitividad tardía.

Otros efectos secundarios que se pueden ver con sarampión son los siguientes: fiebre moderada que puede ocurrir durante el mes posterior a la inmunización. Generalmente una erupción, fiebre o ambas surgen de cinco a doce días después de la inmunización. Cuando ocurre la erupción, esta es usualmente mínima y generalizada. Aún más serio parece ser el número de casos de desórdenes neurológicos que ocurren después de vacunar con la vacuna viva de sarampión (45). Desde 1971 al 1973 se reportaron en los Estados Unidos 84 casos de desórdenes neurológicos con un comienzo menor de 30 días después de administrar la vacuna de sarampión viva. Trece de éstos podían ser clasificados como casos relacionados a otra cosa que no fuese

la vacuna y otros once eran convulsiones febriles no complicadas posiblemente relacionadas a la vacunación. Un caso llenó los criterios para panaencefalitis esclerosante subaguda (46). Los otros 59 demostraron hallazgos clínicos de encefalitis y encefalopatía. La causa pudo ser establecida, pero 45 o el 76 por ciento tuvo comienzo entre 6 a 15 días después de la vacunación. Este agrupamiento de casos sugiere que algunos puedan estar relacionados a la vacuna. La incidencia de desórdenes neurológicos reportados es de 1.16 casos por millón de dosis de vacuna.

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UNDIFFERENTIATED CARCINOMA OF THE THYROID: CASE REPORTS AND REVIEW OF THE PUERTO RICO CANCER REGISTRY EXPERIENCE FROM 1970-1974

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Juan Velázquez Vera, MD and Jorge A. Moscol, MD

Summary: The case reports of two patients recently seen by us with undifferentiated carcinoma of the thyroid are presented. The pathological criteria for the diagnosis are reviewed. The experience reported by the Puerto Rico Cancer Registry, from 1970-1974, with this usually aggressive malignancy is also presented.

Resumen: Dos casos tratados recientemente por nosotros con carcinoma no diferenciado de la tiroide son presentados. Los criterios patológicos de este diagnóstico son revisados; también se presenta la experiencia reportada al Registro de Cáncer de Puerto Rico (1970-1974) de carcinoma del tiroide.

Introduction

The incidence of carcinoma of the thyroid in Puerto Rico was 3.9 cases/100,000 population in 1975 (8), being almost identical to the incidence in the United States where it is 3.8 cases/100,000 population (4).

The histologic classification of thyroid cancer that we find most applicable is the division into 1) differentiated carcinoma, 2) medullary carcinoma, and 3) undifferentiated carcinoma. In the first group of differentiated carcinomas of the thyroid, papillary and follicular carcinomas are included and these make up for about 75 percent of all thyroid cancers. The undifferentiated can be subdivided into small cell and large cell.

The degree of undifferentiation has been found to have a direct relationship with mortality. The survival has been found to correlate clearly with the tumors' histologic type (5).

The 10 year-survival for papillary carcinoma of the thyroid is more than 80 percent, and for follicular carcinoma is about 50 percent. The 5 year-survival for undifferentiated carcinoma of the thyroid is much less and has been reported as 16 percent (5). Many patients with this very aggressive malignant tumor live only a few months after the diagnosis.

Aldinger, et al, reported the experience at the M.D. Anderson Hospital with 84 cases of spindle and giant cell carcinoma of the thyroid seen from the period 1949 to 1977, with 7.1 percent 5 year-survival and a mean survival of 6.2 months from the time

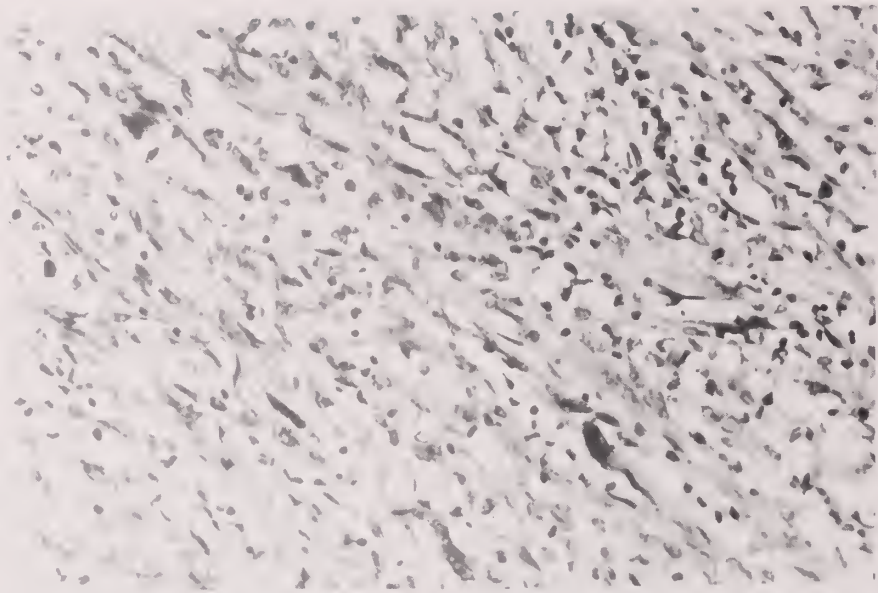


Figure 1: Undifferentiated carcinoma, Giant cell type, with many bizarre nuclei and with many spindle cells, giving a sarcomatous appearance.

of tissue diagnosis (1).

S. Rafla reported the 15-year experience of the Manitoba Cancer Foundation. He reported 38 cases, 11 percent of all thyroid malignancies, with anaplastic tumors (10).

The purpose of this paper is to review the pathological criteria for the diagnosis of undifferentiated thyroid cancer; to present 2 cases recently seen by us; to review the P. R. Cancer Registry experience reported from 1970-1974 with carcinoma of the thyroid; and to comment on the multi-modal approach that we feel is needed to try to improve the results with the management of this tumor.

Case Report No. 1:

This 63-yr-old female was first admitted to the University District Hospital on February 20, 1979 with a history of a rapidly growing mass in the right

side of the neck. The patient had developed anorexia and had lost 14 pounds of weight in one month.

Physical Examination: On admission the patient had a large 5 x 7 cm mass in the right supraclavicular area and another 2 x 2 cm node in the right upper jugular area.

A biopsy of the right supraclavicular mass was done on March 26, 1979 and revealed undifferentiated anaplastic giant cell carcinoma of the thyroid with muscle extension (Fig. No. 1 and Figure No. 2).

Radiotherapy was given from April 19, 1979 to May 18, 1979 and the patient received 5,000 rad to a field of 24 x 19 cms encompassing neck and mediastinum.

At the end of radiotherapy there was about a 50 percent reduction in the neck mass; but the size of the pulmonary metastasis grew from 3.0 x 2.5 cm on April 14, 1979 to 5.5 x 4.5 cm on May 16, 1979.

Patient was referred for chemotherapy at the end of radiotherapy.

On June 13, 1979 the patient died at home.

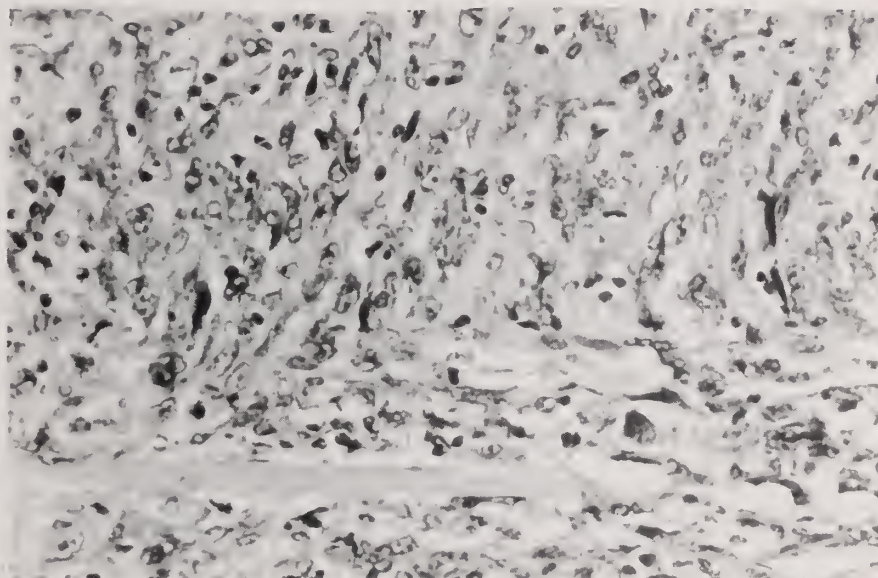


Figure 2: An anaplastic, pleomorphic tumor with many mitotic figures and infiltration of skeletal muscle.

Comments:

The tumor doubling time (T.D.T.) (6, 7) of this anaplastic thyroid cancer calculated from the change in size of the chest tumor nodules was about 8 days. This definitely makes this malignancy one of the most aggressive known to man.

The survival from the time of histologic diagnosis was only 79 days.

Case Report No. 2:

On December 5, 1978 a 68-yr. old female was referred to the Radiotherapy Institute at the Metropolitan Hospital after an emergency tracheostomy done at another hospital where she presented with severe upper airway obstruction.

A biopsy was done on November 28, 1978 which showed an anaplastic carcinoma of the thyroid; giant cell type.

On physical examination the patient showed a large, hard thyroid mass measuring 8 x 6 x 5 cm.

The chest x-ray showed some mediastinal widening in the upper thorax.

On December 11, 1978 radiotherapy was started to a field of 14 x 18 cms at 200 rad/day.

On December 26, 1978, patient began to aspirate oral fluids despite a cuffed tracheostomy tube. A tracheo-esophageal fistula could not be demonstrated radiographically.

The patient developed a right upper lobe pneumonia, deteriorated rapidly despite antibiotics and died on December 29, 1978. No autopsy permission was obtained.

Comments:

The survival from the date of diagnosis was 31 days. The mass in the neck responded well to 2,000 rad of radiotherapy given in 16 days. The complication of aspiration and subsequent pneumonitis caused a rapid demise.

Pathological Features

The undifferentiated carcinomas com-

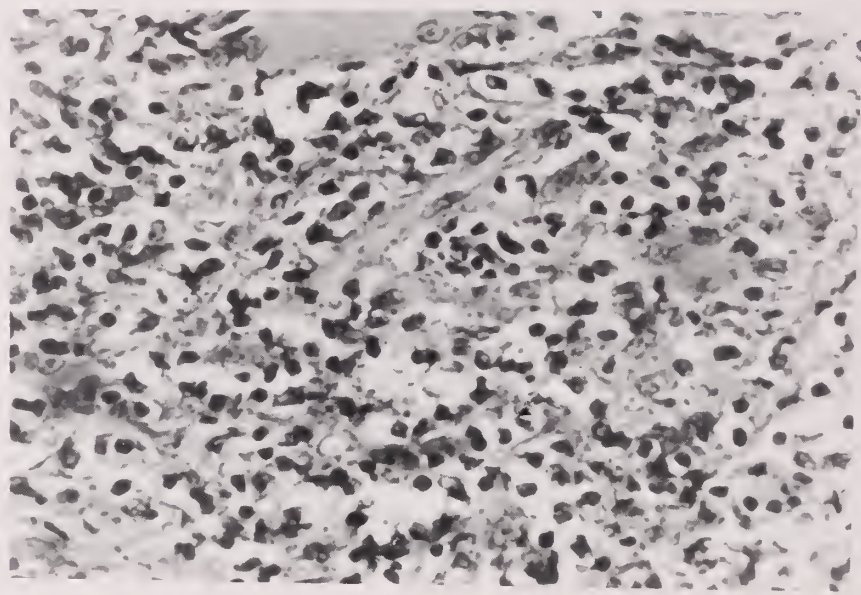


Figure 3: Small cell undifferentiated carcinoma of diffuse type growing into skeletal muscle. No gland formation is observed.

monly involve extensive portions of the thyroid gland and show early infiltration of the adjacent structures, therefore, they become fixed to the trachea, esophagus and skeletal muscles of the neck. This often makes a complete surgical resection impossible.

Histologically, the undifferentiated carcinomas are composed of small round cells, giant cells or spindle forms; they usually form no papillary or follicular structures but these can occasionally be identified. In many instances cellular pleomorphism is observed as well as many mitotic figures. (Figures 1, 2, and 3). Just as follicular and papillary tumors of the thyroid are often mixed, also, the undifferentiated carcinomas may show mixed patterns. In general, two main types are recognized:

1. Undifferentiated carcinoma, small cell type.

The small cell carcinomas are composed of two morphologic types, a compact and a diffuse. The compact type is made of uniformly appearing, small, closely packed cells, which arrange themselves in strands or clusters. The diffuse type resembles malignant lymphoma. To discriminate between these two types of thyroid malignancy, a careful and detailed examination of many parts of the specimen is required and frequently electron microscopy. The cells composing this type of tumor are small, uniformly round and with scanty amount of cytoplasm.

2. Undifferentiated carcinoma, Giant cell type.

The giant cell type is the most frequently encountered, in our experience. It is a growth showing numerous giant cells, fre-

TABLE I

Undifferentiated Carcinoma of the Thyroid

Cases Reported to the Puerto Rico Cancer Registry
 with Carcinoma of the Thyroid (1970-1974)

	Cases	Percent
<i>All Histologic Types</i>	207	---
<i>Undifferentiated Ca.</i>	(11)	(5.3)
<i>Male</i>	1	9
<i>Female</i>	10	91

TABLE II

Undifferentiated Carcinoma of the Thyroid
 Puerto Rico Cancer Registry (1970-1974)

AGE DISTRIBUTION

(AGE SPAN = 50 - 94)	Age (Yrs.)	No. Cases
	41 - 50	2
	51 - 60	1
	61 - 70	1
	71 - 80	5
	81 - 90	1
	91 - 100	1
	TOTAL -	11

quently mixed with spindle cell elements. Giant cell carcinoma of the thyroid suggests origin from a pre-existing benign tumor or low grade carcinoma (1, 3). There is clinical as well as microscopic evidence for this statement.

Ashley states (2) that the presence of ill-formed acini or papillary processes, however, must not be taken as absolute evidence that this type of tumor has developed through a process of de-differentiation of a follicular

TABLE III
Undifferentiated Carcinoma of the Thyroid
Puerto Rico Cancer Registry (1970- 1974)

SURVIVAL	
<i>Case No.</i>	<i>Survival (Mos.)</i>
*1	72
2	6
*3	14
4	5
5	4
6	1
7	4
8	4
9	9
10	8
11	5

Ave. Survival (months) = 5.1

**(excluding case No. 1 and No. 3)*

3 Year-Survival = 9 percent

(1/11)

nor papillary carcinoma, although such transmutation is possible.

P. R. Cancer Registry Experience (Reported 1970-1974) With Carcinoma of the Thyroid

A total of 207 cases were reported to have carcinoma of the thyroid from 1970-1974. Of these, only 11 cases (5.3 percent) were reported as undifferentiated carcinomas of the thyroid (Table I).

The sex distribution showed that 91 percent of these 11 cases were female (Table I).

The age distribution showed most cases were in the eighth decade of life (Table II).

The average survival of the 11 cases is shown in Table III. The 3 year-survival was found to be only 9 percent.

The slides of the cases with undifferentiated carcinoma of the thyroid were not available for review.

Discussion

The pathological criteria for undifferentiated carcinoma of the thyroid have

been reviewed. We feel the histologic diagnosis should be made by two independent pathologists, making sure that lymphoma of the thyroid, with which small cell undifferentiated carcinoma of the thyroid is confused, is excluded. Survival of 1^o lymphoma of the thyroid has been reported to be 38 percent at 4 years (9).

In view of the poor prognosis of this very aggressive malignancy as shown in our 2 case reports and in Table III, a multimodal approach should be used in management. Surgeons, radiotherapists, and medical oncologists should cooperate in the management of undifferentiated carcinoma of the thyroid to attempt to improve on the 9 percent three-year survival (Table III).

We feel maximal surgical removal of the mass in the neck should be attempted, when feasible, for debulking, even when resection is incomplete. This should be followed by radiotherapy to the primary tumor and regional node area for a dose of 5,000 rad in 5 weeks with 150 to 200 rad fractions and a boost of 1,000 rad to the surgical area. If gross tumor remains after surgery, the total dose should be 6,000 to 7,000 rad.

In the future, radiosensitizers such as misonidazole may be used to enhance the radiobiologic effect of conventional radiotherapy on the local control of hypoxic tumor cells. Also, multidrug chemotherapy should be used after radiotherapy to tackle the problem of dissemination. Actinomycin D in addition to surgery and radiotherapy has been shown to improve results (11). It is controversial which drug combination is best, but some authors claim improved survival with combination chemotherapy including melphalan, adriamycin, bleomycin, and vincristine

plus radioiodine. In view of the rarity of this malignancy, there are no controlled trials comparing treatment modalities.

Acknowledgments

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The incidence of peptic ulcer in about 3000 patients treated up to two years in clinical studies was about 1 in 50. Thirty-four percent of the ulcer patients had prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs, including corticosteroids, known to produce peptic ulceration.

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Cardiovascular:—edema, about 1 in 15 patients; hypertension, less frequently.

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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MEDI QUIZ - RENAL MEDICINE

Answers:

1. Answer is B. Symptoms are variable, as indicated. However, such symptoms do not correlate closely with either the magnitude or duration of the hyponatremia. Treatment is with hypertonic saline, alone or with Lasix®. Data from experimental animal studies suggests good correlation between symptoms and the interplay of a net increase in brain water and a loss of brain electrolytes.

Reference: Medicine 55: 121-129, 1976.

2. Answer is E. All of those listed *except* growth hormone have been implicated as mediators of renal water excretion.

Reference: NEJM 292: 81-8 and 141-5, 1975.

3. Answer is E. In the hyponatremic patient, SIADH is suggested when the urine is inappropriately hypertonic to plasma. However, it is essential to exclude other disorders that mimic this serum and urinary electrolyte picture. Recently, hypouricemia has been reported as an important clue to the diagnosis of SIADH. Once the diagnosis is established, a careful drug history is essential, as a wide variety of therapeutic agents can cause this syndrome. If the patient is stable and does not require the use of hypertonic saline, he may be treated with fluid restriction; if that is intolerable or ineffective, demeclocycline, which interferes with ADH action and is generally well tolerated, may be added.

Reference: NEJM 298: 173-7, 1978; Kidney Int 10: 38-45, 1976; NEJM 301: 528-30, 1979.

4. Answer is B. A recent study found that the combination of rapid sequence IVP, upright resting plasma renin, and the

presence or absence of a systolic and diastolic abdominal bruit has better than 90 percent sensitivity and specificity for establishing the presence of renovascular hypertension. The addition of saralasin infusion failed to increase diagnostic yield.

Reference: Ann Int Med 91: 617-622, 1979.

5. Answer is C. All of the causes of metabolic acidosis except renal tubular acidosis (RTA) cause retention of *unmeasured* anions, resulting in a high anion gap. RTA, on the other hand, results from a loss of bicarbonate with elevation of serum chloride, such that the anion gap is not increased.

Reference: NEJM 297: 814-817, 1977.

6. Answer is A. Urinary osmolality, sodium, and urine-to-plasma creatinine ratio are useful in distinguishing pre-renal azotemia, a potentially reversible cause of oliguria, from oliguric and nonoliguric acute renal failure. Pre-renal azotemia is likely with urine osmolality greater than 500 mOsm/kg, urine sodium less than 20 mEq/L, and urine-to-plasma creatinine ratio greater than 40. Conversely, acute tubular necrosis is suggested by urine osmolality less than 350 mOsm/kg, urine sodium greater than 40 mEq/L, and urine-to-plasma creatinine ratio less than 20.

Reference: Ann Int Med 89: 47-50, 1978.

7. Answer is E. Acute renal failure has been reported with a great variety of diagnostic x-ray procedures, including intravenous urography, angiography, and oral and intravenous cholangiography. Factors that predispose patients to this com-

plication include diabetes mellitus, dehydration, and the presence of underlying renal disease. The latter appears to be the most important predisposing condition.

Reference: Nephrology 17: 28-40, 1976.

8. Answer is B. Pre-existing cardiac disease or arrhythmia is present in most patients with renal artery emboli. Initial symptoms include flank pain, abdominal and chest pain, nausea and vomiting. Features in the clinical and laboratory evaluation that support the diagnosis are leukocytosis, fever, proteinuria, hematuria, and elevated levels of serum lactic dehydrogenase, serum glutaminoxalacetic transaminase, serum glutamin pyruvic transaminase, and alkaline phosphatase. The presence of red blood cell casts would be indicative of glomerulonephritis.

Reference: Ann Int Med 89: 477-482, 1978.

9. Answer is D. The most likely diagnosis is chronic interstitial nephritis, which is associated with many causes, including analgesic abuse (most common), hypercalcemia, stones and urinary tract abnormalities with resulting obstruction and infection, sickle cell disease, nephrosclerosis, and renal tuberculosis. Chronic glomerulonephritis, on the other hand, usually (but not always) presents with more significant proteinuria as part of the nephrotic syndrome, urinary casts, and renal hypertension, as well as azotemic renal failure.

Reference: Ann Int Med 82: 453-459, 1975.

10. Answers are A-3, B-1, C-5, D-6, E-4, F-2. Most syndromes resulting in renal failure can be caused by drugs or other environmental agents. Amino-

glycoside antibiotics have been associated with the development of acute tubular necrosis, both oliguric and, more commonly, nonoliguric. Toxicity correlates with serum drug levels greater than 12ug/ml. Lasix®, along with extracellular fluid volume depletion, may enhance toxicity. Methysergide is an unusual cause of extrarenal obstruction, through the development of retroperitoneal fibrosis. Amphetamines cause a necrotizing angitis. The triad of oliguric acute renal failure, severe hypertension, and a history of intravenous drug abuse should suggest this diagnosis. Penicillins and semisynthetic penicillins have been implicated in the development of acute interstitial nephritis. One to two weeks after drug exposure, patients with this syndrome frequently have fever, pruritic morbilliform rash, gross and microscopic hematuria, and decreasing renal function without oliguria. The disease is reversible when the drug is withdrawn. Intravenous heroin use may produce nephrotic syndrome, characterized by massive proteinuria, hypoproteinemia, edema, and hyperlipoproteinemia. Finally, analgesic compounds containing acetaminophen, aspirin and phenacetin in combination are the most frequent cause of chronic interstitial nephritis. These patients present with chronic complaints that require analgesics (such as headaches and back pain), manifestations of chronic renal failure, anemia, pyuria, infection, or obstruction, depending on the presence of papillary necrosis.

Reference: Ann Int Med 82: 582-590, 1977.

11. Answer is E. Although hypokalemia (serum potassium < 3.5 mEq/L) is often

suggestive of primary hyperaldosteronism in the hypertensive patient not on diuretics, up to 20 percent may have K^+ between 3.5 and 4.0. Serum sodium > 140 mEq/L also favors the diagnosis; but the hallmark of this syndrome is the demonstration of the autonomy of aldosterone secretion, through demonstration of the inability to stimulate plasma renin activity by volume depletion, and to suppress aldosterone secretion by sodium loading.

Reference: *Ann Int Med* 90:386-395, 1979.

12. Answer is C. Insulin resistance with abnormally high serum insulin levels and elevated serum growth hormone levels, gastrin levels, and parathyroid levels are seen in uremia. Most uremic patients are *euthyroid* despite the presence of abnormal thyroid function tests.

Reference: *Medicine* 54: 345-375, 1975.

13. Answer is A. Hypertension in dialysis patients is a common management problem. Often it is volume dependent, related to sodium and water retention, and may respond to increased dialysis. However, sometimes (depending on the underlying renal disease) the kidneys themselves perpetuate hypertension by renin production. In the past this was

treated by nephrectomy; current treatment is with potent vasodilators, such as minoxidil.

References: *Arch of Int Med* 133: 1059-1066, 1974.

NEJM 289: 167-171, 1973.

14. Answer is E. Membranous glomerulonephritis, a common cause of glomerular disease in adults, is often idiopathic but can be associated with underlying systemic disease, such as cancer or systemic lupus erythematosus. Recent reports indicate a degree of steroid responsiveness, and a trial of such therapy may be helpful.

Reference: *NEJM* 290: 257-266, 313-319, and 374-381, 1974.

15. Answer is B. Nonoliguric acute renal failure is an important entity to recognize because it has a better prognosis than oliguric acute renal failure. It has the same urinary diagnostic indices as oliguric acute renal failure and is frequently associated with the use of aminoglycosides. The use of Lasix® early in the course of oliguric acute renal failure may cause conversion to the nonoliguric condition, and is generally worth a trial because of the improvement in prognosis and greater ease in fluid management.

Reference: *NEJM* 290: 1134-1138, 1977.

TREATMENT OF PITUITARY HYPERFUNCTION WITH PROTON BEAM IRRADIATION: UNIVERSITY REGIONAL HOSPITAL EXPERIENCE

Francisco Aguiló Jr., MD, FACP

Introduction

Surgery and external irradiation remain the two basic modalities of therapy for pituitary disease. Radioimmunoassay techniques have provided earlier and more specific means of diagnosing various pituitary lesions, while more sophisticated radiological methods allow for easier and more precise recognition of such lesions. These advances in diagnosis have been assisted by improved surgical techniques, such as the transphenoidal approach utilizing the dissecting microscope (1), as well as by additional alternatives for more effective delivery of radiation, such as the proton beam (2). Our initial experience with the latter is the basis of the present report.

Materials and Methods

Four patients from the Endocrinology Service of the University Regional Hospital (URH) and 3 private patients comprise the study group. There were 5 females and 2 males, whose ages ranged from 23 to 55. Their initial and subsequent evaluation was carried out at our institution or privately, utilizing conventio-

nal laboratory and radiological means. Special samples utilizing radioimmunoassay techniques were performed at our Radioimmunology Laboratories (growth hormone, insulin) or at the Nichols Institute in California (prolactin, ACTH, TSH, LH, FSH, PTH). Plasma cortisol measurements were similarly done at the Nichols Institute or Reference Laboratories while urinary 17-hydroxy (17-OHS— and 17-keto-steroids (17-Ks) were done at our Endocrine Laboratory by standard Porter-Silber and Zimmerman methods respectively. Triiodothyronine resin (T_3R) and total thyroxine (TT_4), were performed at the Interlab Laboratory. Automated procedures as per multi-channel autoanalyzer were done for all routine laboratory determinations including complete blood counts (CBC), urinalyses, blood indices (MCV, MCH MCHC) and SMA-13 comprising: SGOT, alkaline phosphate, uric acid, serum phosphate, creatinine, cholesterol, bilirubin, total protein, albumin, calcium, LDH, urea and glucose (by hexokinase reaction). Serum electrolytes were determined by flame photometry. All of these tests were done at the Central Laboratories of the Puerto Rico Medical Center.

The pituitary diseases presented by these patients comprised: 4 with Cushing's, 2 with prolactinomas and one acromegalic.

Upon completion of the pertinent diagnostic work-up the patients were referred to the Massachusetts General Hospital in Boston, Mass., for definitive therapy with the proton beam (PBIr). This was administered between September 1976 and May 1979. The dose given varied from 6,100 to 14,500 rads; the average dose being 9460 rads. Follow-up has been carried out by our staff at the URH or by myself and it spans from 8 months to 3 years.

In most cases monetary assistance was provided for the patients by various agencies such as Vocational Rehabilitation and Teacher's Association.

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TABLE I

Proton Beam Irradiation for Pituitary Hyperfunction - URH

<i>Patient No.</i>	<i>Age</i>	<i>Sex</i>	<i>Diagnosis</i>	<i>Duration</i>	<i>Month & Year PBIr</i>	<i>Outcome</i>	<i>Dose and Comments</i>
1	43	F	mild Cushing's	3 yr?	9/1976	Cured	14,529 r
2	33	F	mild Cushing's	2 yr?	6/1977	Cured	14,100 r
3	55	F	moderate Cushing's	3 yr?	3/1977	Ptosis O. D. 2 mo. post PBI; recovered in 2 yr.	12,489 r 1 yr. later, Bilat. AdrenX
4	23	M	Acromegaly	5 yr.	11/1977	Initially worse, x 2 mo; Improved in 8 1/2 mo.	11,000 r
5	41	F	severe Cushing's	10 yr.	7/1978	worse; then died	11,000 r ? CHF from uncontrolled ↑ B.P.
6	29	F	Prolactinoma	18 yr.	6/1978	Initial improvement. ↓ Prol. 6 mo. ↑ Prol. 14 mo.	8,000 r 1 ^o Amenorrhea persisted
7	32	M	Prolactinoma	9 yr.	1/1979	Better x 3 mo; then worse; blind and hypopit. post T. P. H. X 3	6,100 r Suprasellar Ext. ↓ VF 3 mo. post irr.; T.P. H. x 3



Figure 1: Pre and post proton beam irradiation appearance of Case 1.

Case Reports

Table I summarizes the highlights of these patients.

Case 1:

AHB, a 43 year-old white female was first seen on June 28, 1974 complaining of a 60 pound (27.3 kg) weight gain during the last 6 years. She also complained of "lumps" on her body, notably on her shoulders. There had been recurrent episodes of thrombophlebitis of both legs, more common in the left one, during the preceding 5 years, com-

plicated on 2 occasions by pulmonary emboli, the most recent one 4 months previously. She was a heavy smoker of 3 packs of cigarettes per day, for the past 20 years. For the preceding 3 years, she had noted a tendency to retain fluid, associated with menstruation. For the previous 2 years, she noted increased sweating and urination. There was a family history of diabetes mellitus in an older sister, of an insulin-dependent type. On physical examination she had a B. P. of 150/80, pulse 92 per minute, regular. Initially, she only presented with obesity; (145 lb. or

65.9 kg for a 60.5 inches or 1.54 m frame). Six months later her right shoulder "fullness" was followed by a similar finding on her left supraclavicular area, and bilateral small abdominal striae appeared which had been absent before. Her B. P. had increased to 170/100 and a mild plethoric look was present. The initial radiological and laboratory studies were all normal, except for a reduced one-second forced expiratory volume (76 percent of that predicted). By January 1975, her 24 hr. urinary 17-OHS was borderline high (10.5 mg/d), with normal plasma cortisol (9 ug/dL, normal 8-20). Because of excessive menstrual flow, dicoumarol treatment had to be stopped and a hysterectomy was performed on Nov. 10, 1975. By January 1976 her skin was thinner and her abdominal striae had turned more reddish. A repeat 24 hr. urine 17-OHS steroids was 24.3 mg/day, increasing to 75 mg post ACTH stimulation (40 units I.V. x 8 hours). After Metopirone, the 24 hr. urinary 17-OHS increased to 106 mg. Upon low-dose dexamethasone (2 mg/day x 2 days), it dropped to 0.5 mg. An oral glucose tolerance (100 Gm dose) turned out "diabetic" (initially normal). Lateral skull and PA chest films remained negative. A pneumoencephalogram was also normal. A diagnosis of ACTH dependent Cushing's was made and the patient was referred for therapy to Boston. There she received 14,529 rads on September 21, 1976.

Course:

In 2 months, the 24 hr. urinary 17-OHS was normal; 11 months post PBIr she had had a 37 lb (16.8 Kg) weight loss and by 14 months post irradiation, there were no clinical stigmata of Cushing's disease. The patient has been doing well during a 3 year follow-up (Figure 1).

Comment:

Excellent results were obtained in early mild Cushing's. Subsequent investigation of pituitary reserve revealed: normal ACTH reserve (post-metopirone 17-OHS: 13.1 mg from 4.2 mg/d baseline); normal ACTH (49 pg/ml); normal LH (20 mIU/ml) and FSH (22 mIU/ml) in non-oophorectomized subject); normal TSH (2.9 uIU/ml), T-3R (29.5 percent) and TT4 (9.3

ugm/dL).

Post-insulin-induced hypoglycemia failed to increase human growth hormone (hGH) over 1 ng/ml. Thus, her pituitary function was only affected regarding growth hormone reserve.

Case 2:

MDS, a 33 year-old white female, had had gradually increasing weight and hypertension of 2 years duration, when first seen at the URH in October 1976. There had also been headaches, increased thirst and polyuria, plus occasional non-specific joint pains without swelling, for the preceding few months. She considered her personal life stressful on account of an unpredictable husband and 4 small children, plus her full-time job as a registered nurse supervisor. On physical examination she presented with a typical Cushing's facies and truncal obesity, without striae. B. P. 160/110; pulse 88 regular. She weighed 156 lbs (70.9 Kg) and was 61 inches (1.55 m) tall. Routine laboratory tests and radiographs were normal or negative. An oral glucose tolerance showed diabetes. The baseline urinary 17-OHS was elevated (12 to 14 mg/24 hrs.); urinary 17-Ks (4.7 mg/d), was normal. After 2 mg dexamethasone 17-OHS suppressed to 5.9 mg/d and to less than 2 mg with high dose dexamethasone (8 mg). Upon ACTH infusion (40 units x 8 hrs. I.V.) 17-OHS increased to 39 mg/24 hrs. Serum ACTH was normal (64 pg/ml in AM) and decreased to 21 pg/ml after low dose dexamethasone. The pneumoencephalogram was not remarkable. Hypertension was treated with diuretics and 1 Gm of alpha-methyl dopa daily but was not adequately controlled until definitive therapy was instituted. This was carried out on June 6, 1977 at Mass. Gen. Hospital giving 14,100 rads. In 5 months she had lost 20 lbs (9.1 Kg) and baseline urinary 17-OHS was practically normal (8.5 mg/d; top normal 8 mg/d). Within a year, antihypertensive therapy had been discontinued and she felt back to "normal" as far as her body and dress size. However, she continued having headaches, poor memory and a sense of "fullness" and heaviness in her head (which she attributed to PBIr).

Her glucose tolerance, initially "diabetic", was borderline 6 months post PBIr and became normal one year later. The metyrapone ACTH reserve



Figure 2: Close-up of Case 2 prior to therapy. Note moderate facial hirsutism.

test done 28 months post PBIr revealed a normal baseline 17-OHS (3 mg per 24 hrs), increasing to 17.7 mg/24 hrs. Serum TT4 (4.8 ug/dL) and T3 R (44 percent) remained normal. After a hysterectomy and bilateral oophorectomy done in 1975, she has continued to require small doses of conjugated estrogens (0.6 mg/d) for her "flushes and flashes".

Comments:

Again, very good results and "cure" of Cushing's disease, of rather mild intensity. Post propranolol-exercise hGH stimulation showed no increase above 0.7 ng/ml. Thus again, pituitary reserve only lacked hGH.

Case 3:

MRR, a 55 year-old white female, was seen in consultation because of weakness, increased facial hair and ecchymoses of 3 years duration. She attributed her symptoms to hormones (conjugated estrogens) given elsewhere to her 3 years previously, after removal of a uterine fibroma (and oophorectomy).

Electrolytic removal of facial hair failed to help her and caused infection. In the past 2 years she had gained 11 pounds (5 Kg). She had noted increased fluid retention for which chlorothiazide had been given 2 years previously. Four months prior to her first visit, hypertension was diagnosed elsewhere and she was started on 1 Gm of alpramethyl dopa daily. Past history revealed chronic glaucoma of 20 years duration, treated with pilocarpine drops. On physical examination she appeared plump, with increased facial hair (Figure 2). B. P. 140/100 P, 80/min., regular. Weight: 127lb (57.7 Kg) and height: 58.5 inches (1.48 m). Her right eye had mild proptosis (21 mm vs 18 mm exophthalmometric reading). Atrophic skin was noted, especially over both arms, with the presence of several ecchymotic areas. Lungs and heart were normal. A mid-abdominal surgical scar had become wider and more pigmented according to the patient. A few thin non-violaceous striae were noted bilaterally on the abdomen. Her back presented with a mild degree of "buffalo hump". A severe onychomycotic infection of various toes and both thumbs was present. Routine laboratory examinations were negative or normal, including an oral glucose tolerance. Osteoporosis was seen in lumbosacral films. There was a right upper lobe pulmonic granuloma. The PPD was negative. The Ba enema revealed a few sigmoidal diverticuli. Gall bladder examination revealed cholelithiasis. Basal urinary 17-OHS which averaged 15 mg/24 hrs, increased after ACTH (40 units x 8 hrs. I.V.) to 89 mg/d. There was a fall of 17-OHS upon low dose dexamethasone (to 9 mg/d, but no further decrease after 8 mg x 2 days. 8:00 AM cortisol was increased (26 ug/dL), and unchanged at 8:00 PM (28 ug/dL). Plasma ACTH was normal (45 pg/ml) and unchanged in PM (48 pg). Post dexamethasone, ACTH was unchanged (42 pg/ml). From the above studies, indicating hyperresponsiveness to exogenous ACTH, but failure to suppress with high dose dexamethasone, it was suspected that she could have adenomatous hyperplasia of the adrenals. In the interest of finding out how much improvement of hypercorticism could be achieved by treatment directed at the pituitary, proton beam therapy was recommended. (She was told that most likely, adrenalectomy would have to be done eventually). While she

waited for PBIr, a trial with up to 16 mg cyproheptadine daily was given for one month, without suppression of urinary 17-OHS. On March 8, 1977 PBIr, at a dose of 12,489 rads, was given to the pituitary. Two months later she developed a rather sudden onset of ptosis of the right eye. There was associated diplopia. Ophthalmologists recommended a trial with Mestinon, 60 mg t.i.d. to no avail. Reevaluation 6 months post proton beam, confirmed persistence of hypercorticism (mean urinary 17-OHS 15.5 mg/d), with serum cortisol 25.6 ug/dL in AM and 23.8 ug/dL in PM. Plasma ACTH remained normal at 73.4 pg/ml of 8:00 AM and elevated (78.6 pg/ml at 8:00 PM. This time, dexamethasone did suppress serum cortisol to 18.3 and ACTH to 37.5 pg/ml. Encouraged by such findings, a new trial with cyproheptadine of up to 32 mg per day was carried out, but the serum cortisol and urinary 17-OHS stayed elevated, even though the ACTH dropped to 19.7 pg/ml. As there was no clinical response and her urinary 17-OHS stayed high (18.8 mg/d), such therapy was abandoned after a 2 month trial. It was recommended that an adrenalectomy be performed with the goal of curing her disease. Bilateral total adrenalectomy was performed March 2, 1978, at the Mass. Gen. Hospital. Surprisingly for us, "mildly atrophic adrenal glands" were described; not in keeping with the reported weights: adrenal weights of 5 Gm. (right) 6 Gm. (left). Replacement therapy was started with 37.5 mg cortisone acetate and 0.1 mg 9-alpha-fluorhydrocortisone, but this kept the patient hypertensive. Therefore, we gradually decreased the dose and finally discontinued Florinef all together. Approximately 2 years after PBIr, her unilateral ptosis disappeared, along with her diplopia. Four months after stopping Florinef her antihypertensive medications could be discontinued and she has remained normotensive since. A tendency to hyperkalemia disappeared in about 6 months and the feeling of weakness, in about one year post adrenalectomy. She has returned to her usual dress size, feels very well and is able to do all her housework.

Comment:

This patient was closely followed, before and after PBIr, and Cushing's disease persisted un-

abated. It remains unclear to us how her adrenal cortices could be "mildly atrophic". Indeed, her persistent hypercorticism inspite of a decrease in plasma ACTH post PBIr was in keeping with our original contention of probable adenomatous hyperplasia. The patient's pituitary function was evaluated 17 mo. after adrenalectomy. It showed that, while on 37.5 mg cortisone acetate daily, her AM plasma ACTH was slightly elevated (107 pg/ml, normal: 15-100 pg/ml), further evidence that on the basis of a postulated lack of ACTH one would not have expected to find atrophic adrenals. At that same time, LH was 21.7 mIU/ml, T3R 37.3 percent, TT4 6.1 ug/dL and FTI 2.3 ug/dL all within normal limits. GH reserve was not tested; pre-treatment there had not been response to insulin-induced hypoglycemia (maximal rise: 1.2 ng/ml.), probably due to the pre-existing and then still prevalent hypercorticism (9/21/76).

Case 4:

JGA, a 23 year-old male, was incidentally found to have thick features and big hands in March 1977. He had experienced increased libido, and an enlargement of hands and feet for 3 years, which he had attributed to weight lifting. There was no history of headaches. There was a history of diabetes mellitus and hypertension in his father.. On physical examination he was rather short (67 inches, or 1.70 M) but husky (170 lbs. or 77.3 Kg), with an athletic build. Behind a thick beard, there were still discernible signs of acromegaly. B.P. 125/90, P. 80/min., reg. Other than moderate acromegalic features (such as increased size of tongue, No. 16 ring size and increased hand volume of 450 ml), his physical examination was otherwise negative. Radiological examinations revealed a symmetrically enlarged sella (16 x 10 mm), an increased calcaneo-cutaneous thickness (27 mm), and increased sesamoid index ($6 \times 5 = 30 \text{ mm}^2$) at the base of thumbs. Routine laboratory data, as well as glucose tolerance, urinary 17 OHS and 17-Ks, T₃R, TT₄, LH, and FSH were all normal. There was an elevation of: serum phosphate (average, 5.4 mg/dL), baseline hGH (average of 66 ng/ml), post glucose serum hGH (205 ng/ml at 1 hr.), urine calcium excretion (average 270 mg/24hr) and urinary total hydroxyproline (95 mg/24 hrs.). On November 8, 1977 he received 11,000 rads

of PBIr at the Harvard cyclotron. Subsequent close follow-up suggested subjective improvement, like feeling lighter (he lost some weight voluntarily), and sweating less. However, from an objective standpoint, during the 2 month following PBIr the baseline hGH in sad, increased to 60-72 ng range, the 1 hr. post glucose hGH increased to 276 ng/ml.; urine calcium to 318 and urinary hydroxyproline, to 110 mg/24hrs. By 5 months, the post PBIr baseline hGH had dropped to 30 ng, the 1 hr post glucose hGH to 105 ng/ml, and urinary hydroxyproline to 78 mg/24 hrs. One year post PBIr, he was still considered active and his hand volume had increased to 530 ml; baseline hGH was 34 ng/ml and urinary hydroxyproline stayed at 74 mg/24hrs. By March, 1979 (16 months post PBIr) his baseline hGH was 22 ng/ml and the 2 hr. post-glucose value was 90 ng/ml. It was decided to enter him into an experimental protocol with alpha-bromocryptine (Parlodel). He has taken it for 6 months so far; the results of which are now being processed.

Comment:

Because of the close pre and post-PBIr follow-up we were able to detect a transient worsening of his acromegalic parameters within the 2 months following irradiation, without a clinical counterpart. He has nevertheless achieved the fastest rate of improvement we have seen in our series of 22 acromegalics, who have so far been treated by conventional x-ray therapy. Still, at 1-1/2 years post PBIr he is not cured of his disease. There seems to have been a mild amelioration with low dose alphabromocryptine, but suitable interpretation of this awaits results of the metabolic parameters, once he is off alphabromocryptine. It appears that no damage of his other pituitary functions was produced by PBIr, a highly desirable goal at his young age.

Case 5:

JCR, a 41 year-old white female, was obese, hypertensive and had documented diabetes mellitus for at least 3 years, when referred to our institution in April 1978. There had been amenorrhea since 8 years prior to admission, and galactorrhea from 1968 up to 1977. At the onset of amenorrhea there fol-

lowed proptosis, headaches and a 15 lb weight gain. Cushing's syndrome had been entertained elsewhere but urine collections had been erratic and there had been other technical problems in her evaluation. Three months prior to her admission there had been an episode of pulmonary edema attributed to her severe hypertension. Low back pain had also been noted recently. Family history was positive for diabetes mellitus and hypertension. On admission she had full-blown facies of Cushing's (Figure 3), with plethoric appearance, mooning of face and a buffalo hump. B. P. was 220/160, P. 132/min. regular. Height: 60.5 inches (1.54 M) Weight 132.5 lbs (60.2 Kg). Scalp hair was thin and decreased; lanugo hair was present on her face. Skin was thin and showed multiple ecchymoses. There was truncal obesity, and the abdomen had a wide striae on the right lower quadrant. Lungs were clear. The heart was not visibly enlarged, but there was a Gr 2/3 systolic apical murmur. No gallops were noted while at the Clinical Research Center. Neurological examination was negative, including normal extraocular movements and visual fields. Laboratory data revealed hypokalemic alkalosis (K 2.4, CO₂ 40 mEq/L), and hyperglycemia



Figure 3: Frontal appearance of Case 5, showing typical Cushing's features.

(268 mg/dL) with 3+ glycosuria. CBC revealed increased WBC count (13, 200); Hb and hematocrit were normal. SMA-12 was within normals, except for lactic dehydrogenase of 350 units (normal up to 225). Diet control and treatment with NPH insulin, 50 to 60 units daily, decreased her serum glucose to 80-150 mg/dL; potassium replacement was given as potassium gluconate, 20 mEq tid, and her hypertension required increasing doses of alpha-methyldopa, Apresoline and aldactone. Propranolol was kept at a low dose (40 mg/d) because of the previous episode of congestive failure. B. P. stayed at about 150/100 to 170-110 mmHg. Radiological examination revealed an enlarged sella turcica; chest film was normal, but spine series revealed diffuse osteoporosis. An EKG revealed left axis deviation and suggested left ventricular hypertrophy by voltage criteria.

Endocrinological evaluation confirmed severe hypercorticism; baseline 24 hr urine 17-OHS were 40-58 mg and 17-KS 17-19.5 mg. Morning ACTH was elevated, at 154 pg/ml. Dexamethasone, 8 mg. daily for 2 days did not suppress the 17-OHS, but did on 16 mg of dexamethasone, to 7.5 mg. Post Metyrapone, 17-OHS increased to 240 mg/day and after I.V. ACTH infusion, 158 mg. Prolactin (10 ng/ml), LH (7.7), FSH (4.3 mIU/ml), TT4 (6.2 ug/dL) T3R, (35 percent), FTI (2.2) were all normal. A pneumoencephalogram failed to reveal extrasellar expansions. On July 25, 1978 she received 11,000 rads to the pituitary during PBIr. She developed a compression fracture of T-11 which produced much discomfort and required analgesics. When seen on 8/2/78 her BP was 130/90, and P. 80 (in spite of having had another episode of pulmonary edema on 7/1/78 and being admitted elsewhere and treated with bed rest for one week). One month post PBIr her B. P. was 130/80, p. 92 on the same antihypertensive treatment, but when last seen 2 months later the B. P. was again back to 160/110. Medications were kept the same: 2 Gm alpha-methyldopa, 200 mg apresoline, 100 mg aldactone, potassium replacement, 40 mg propranolol and 75 units NPH insulin. Her husband came one month later to inform us that she had had a repeated bout of sudden pulmonary edema while off digitalis and had died shortly thereafter at the local health center.

Comments:

This is one of the most severe Cushing's disease we have seen. In spite of early indications that post PBIr, her blood pressure was responding, this was not so when last seen. Indeed, biochemically there was a sustained severe hypercorticism, as judged by her monthly urinary 17-OHS: 72. 5 mg/d, 104 mg/d, 52 mg/d and 92 mg/d on last visit. Chemotherapy with metopirone, op'ddd or aminogluthethimide had been considered, but unfortunately had not been given at the time of her demise. In this case the proton beam failed to produce beneficial results soon enough (4 months) to alter her ominous clinical course.

Case 6:

SMR, a 29 year-old colored female, presented with primary amenorrhea and headaches for the preceding 15 years. She had been evaluated at age 17 for her primary amenorrhea and told that "everything was normal". When given sequential estrogen and progesterone pills, she related these medications with headache and did not take them further. In October 1977 she underwent an exploratory laparotomy elsewhere, and was told to have polycystic ovaries, for which wedge resections were done. After progesterone therapy, she failed to have withdrawal bleeding. There was no history of galactorrhea, but when first seen on Jan. 21, 1978 she had an elevated prolactin of 600 ng/ml. There was a past history of occasional diazepam and ritalin use about 10 years previously. There was a strong family history of diabetes mellitus on her father's side. Her physical examination was essentially negative. There were normal visual fields, a negative neurological exam, normal breasts and no hirsutism. Routine laboratory tests were normal. Radiological findings were limited to a symmetrically enlarged sella turcica (17 x 12 mm). Endocrinological evaluation was within normal: AM cortisol 14 mcgm/dL, TT4 7.9 ug/dL, T3R 31 percent, FTI 2.4; TSH 1.4 uU/ml, plasma testosterone 81 ng/dL (normal: 25-90); urinary 17-KS 13 mg/24 hrs. Repeated prolactin determinations after 3 mos on 400 mg pyridoxine, showed

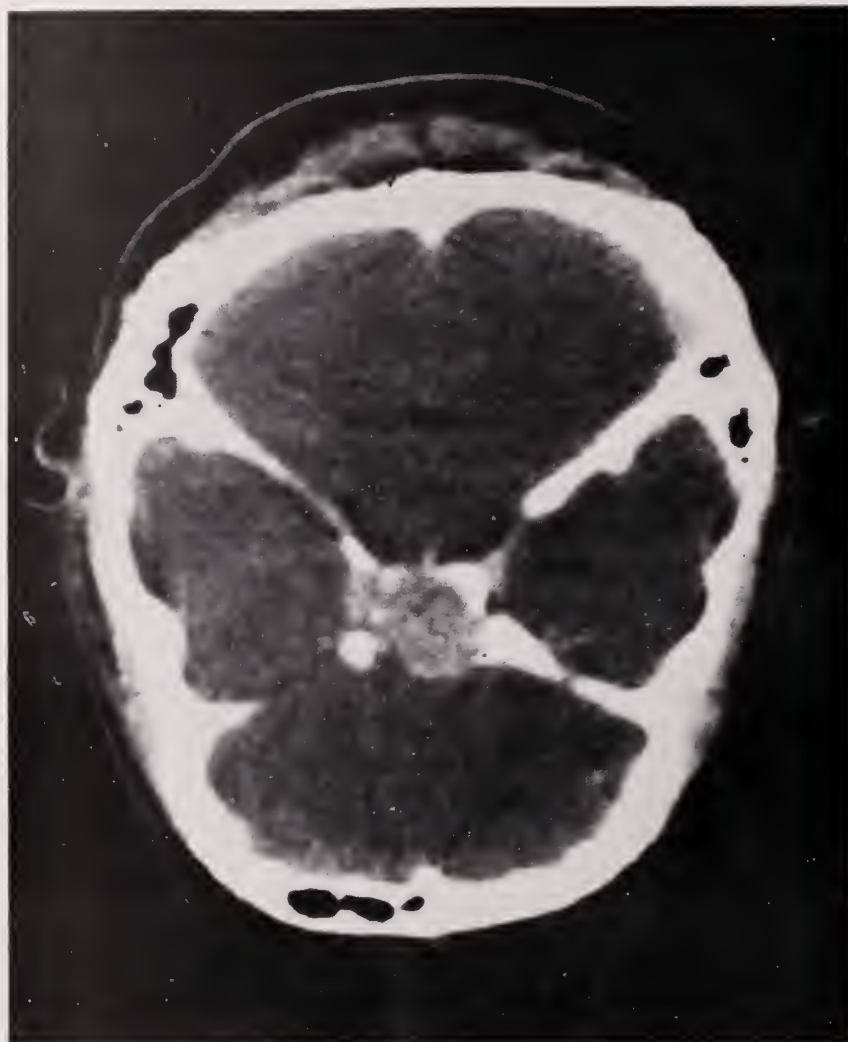


Figure 4: CAT scan of Case 7. Note the extra-pituitary extension of tumor to the left.

no drop. A pneumoencephalogram suggested that the right side of the sella was larger than the left, but there were no suprasellar masses. Pretreatment prolactin: 1100 ng/ml. She was given PBIr, a total of 8,000 rads on June 28, 1978. Although there were no clinical changes, serum prolactin dropped to normal (19 ng/ml) 6 months later, while FSH was normal (9.9) and LH was increased; (35 mIU therefore pointing either to an LH surge or to underlying polycystic ovaries). One year post PBIr her amenorrhea and headaches persisted, and prolactin was again found elevated (over 160 ng/ml). On September 13, 1979, she was

started on slowly increasing doses of alfabromoergocryptine to no avail so far (Jan. 1980).

Comments:

As judged by urinary 17-OHS, TT4, T3R and insulin-induced hypoglycemia, her pituitary function remains intact, but her hyperprolactinemia is unabated. In spite of the large sella the pneumoencephalogram and CAT scan do not support a mechanism of hypothalamic compression, but rather, point to a prolactin-producing adenoma of considerable

size. She is interested in the possibility of getting married and becoming fertile, thus, the next step would appear to be selective transphenoidal hypophysectomy.

Case 7:

MVB, a 32-year old white male, presented with headaches and impotence of 9 years duration. Impotence had been total for the past 5 years, along with increasing lethargy, weakness, fatigue, irritability and mood changes. He had gained about 65 lbs. since he got married 11 years previously. He had not fathered children. About 2 months prior to his referral to the URH, he was seen by a neurologist, for what seems to have been post-Dengue-fever leg paresthesias. Skull films at that time revealed a markedly enlarged sella turcica. On physical examination he appeared pale and puffy. Ht 71" (1.8 M); Wt. 209 lbs. (95 Kg) B. P. 130/85, P. 68, regular. The thyroid gland was not palpable. There was no gynecomastia. Lungs and heart were negative. Genitalia revealed lack of pigmentation, a decreased amount of pubic hair, a normal right testicle (2.5 x 4.5 cm.) but a smaller left one (2.2 x 4.5 cm). His phallus was hypoplastic (7 x 2.5 cm). The prostate gland was of normal size and consistency. Routine laboratory tests were not remarkable. Endocrine evaluation revealed a decrease in thyroid function (TT4 3.8, T3R 27 percent, calculated FT4 1.04 (normal: 1.10-4.40). Baseline hGH: 0.6 ng/ml. FSH was normal (5 mIU) as was the 17-OHS (4 mg/24 hr. urine). Serum testosterone was 642 ng/dL; serum prolactin: 1360 ng/ml. TSH: less than 0.5 uU/ml. A lateral skull film revealed an enlarged sella (25 x 20 mm), which extended suprasellarly by pneumoencephalogram and CAT scan (Figure 4). Visual field examination was normal.

On January 23, 1979 he was given 5000 rads through 6 portals to the pituitary fossa and 1100 rads through 2 portals to the suprasellar area.

The patient was placed on replacement thyroid therapy and did well up to 3 months following PBIr, when he complained for the first time of decreased vision. Bitemporal hemianopsia was confirmed, and he was promptly referred back to Boston, where a transphenoidal hypophysectomy was carried out on May 9, 1979. However, in spite of excellent im-

mediate postoperative results, with the return of full visual fields, the patient had to be re-explored twice: once on June 13, 1979 for the recurrence of decreased vision, increasing headaches, and photophobia, and again on June 29, 1979 due to cerebrospinal fluid leak and meningitis. By that time the prolactin fell to 1.6 ng/ml., plasma cortisol to less than 1 ug/dL, and he was started on steroid replacement therapy. Since the last operation the patient remained blind. Five months after his last surgical procedure, serum prolactin was again found to be elevated: 121 ng/ml. The patient was recently started on alpha-bromoergo cryptine.

Comments:

This has been a most unfortunate case. There was a considerable diagnostic delay and denial concerning his infertility and sexual dysfunction. Then, only 3 mos post PBIr/treatment, necrosis and expansion of the tumor decreased his vision, and finally, his tumor was shown to be relentlessly active, rendering him blind and still presenting a threat to his life.

In a small series of 8 cases with suprasellar extension treated with the "double beam" PBIr, 6 have required no surgery and only one other patient, aside from MVB, has had the need for surgery due to necrosis of the tumor. MVB has so far been the only one with visual impairment. A long-term survey of all proton-treated vs. surgery-treated patients is in process in Boston for computer analysis, in order to ascertain any statistical significance in such management as to final outcome (3).

Discussion

During the past decade, heavy particle irradiation has been added to the therapeutic armamentarium for pituitary disease. This is only available at 2 institutions in the United States where the needed cyclotrons are available: alpha particle irradiation at Berkeley, California, and proton beam irradiation (PBIr) in Boston, Massachusetts. Protons are hydro-

gen atoms from which the single orbital electron has been removed. As compared with X-rays or gamma-irradiation, protons are "heavy", with a mass of 1, whereas those electromagnetic waves have neither mass nor electric charge. By means of a suitable accelerator, such as a cyclotron, a strong magnetic force can make protons achieve high speeds: at the time of ejection, the speed of a proton is one-half as great as the speed of light (2). Although such protons lose some energy in their path, as they stop, they give off more energy than elsewhere along their way; this burst of radiation energy is called the Bragg peak, and the energy of such a peak is maximally utilized in irradiating a discrete organ such as the pituitary. Radionecrosis is therefore induced in the central core of the tumor or gland only. By utilizing 12 delivery routes, most of the brain does not receive radiation. Alopecia and brain necrosis are thus prevented. Usually, a beam diameter is selected so as to leave a shell of normal pituitary gland and thus preserve normal anterior pituitary function. By displacing the beam 2 mm anteriorly, posterior pituitary damage and diabetes insipidus are prevented. The entire procedure lasts from 40 minutes to 2 hours, during which the patient is usually alert and cooperative. A total dose of 5,000 to 14,000 rads is usually given at one sitting. The patient is usually discharged on the second day. Immediate side effects are relatively minor, namely, nausea, vomiting and headaches. The most important, though infrequent long-range complication, has been temporary oculomotor disturbances in about 6 percent of cases (5).

The choice of therapeutic modality in pituitary disease starts by an over-all assessment of the patient, including such factors as: age, sex, functional endocrine status, tumor size, whether neurological signs and symptoms are present, and overall actual and con-

templated benefits vs risks. For functional tumors, that is, those whose secretions give rise to typical clinical syndromes such as acromegaly/giantism, amenorrhea/galactorrhea and Cushing's disease, earlier diagnoses are possible. This is helped by the availability and increased use of more precise and sensitive tests such as radioimmunoassay of various hormones. Among so-called non-functional tumors, size of the tumor at diagnosis is appreciably larger. Thus, in a series of 146 consecutive patients who had a pituitary adenoma removed, 72 percent of the non-functional had an enlarged sella, while only about one fourth of those secreting prolactin and not more than 5 percent of those secreting ACTH caused abnormal sellar area and volume. In the present report, of functional tumors, a higher proportion than just quoted had abnormal sella turcicae. This was largely attributable to neglect or late diagnosis. (Cases 5, 6, 8).

The proportion of patients with Cushing's disease in our present report is larger than expected. In a series of 1,000 pituitary tumors at the Mayo Clinic only 3 percent had Cushing's syndrome while close to 23 percent had acromegaly (7). On the basis of amenorrhea, less than 5 percent could have had undiagnosed prolactinomas in that series; the rest were considered non-functional. Overall, during the past 20 years we have had 22 acromegalic patients, vs. 15 patients with Cushing's syndrome. It is possible that such higher proportion of Cushing's patients is due to more frequent referrals of this type of complicated patient to our "supratertiary" facilities than that of more straight-forward type of well established acromegaly. (It is to be noted that among the 22 acromegalic patients, 4 were incidentally diagnosed by the author elsewhere, which could make the referral proportion almost 1:1 between acromegalic and Cushing's patients).

It should also be noted that the increasing recognition of unapparent microadenomata causing Cushing's disease, as well as the significant recurrences, mortality and morbidity of adrenal surgical approach, have in recent years favored pituitary-directed therapy for ACTH-dependent Cushing's than previously used. Similarly, the increasing recognition of previously unsuspected prolactinomas causing female infertility, as well as male infertility and impotence (8) have contributed a previously unforeseen number of prolactinomas into the series of pituitary tumors. This has also been aided enormously by the commercial availability of prolactin radioimmunoassays. Hence, our two patients in the present report.

In the Massachusetts General Hospital series of patients treated with PBIr (2, 4, 5) the following proportion of diagnoses was found: Acromegaly: 254; Cushing's: 65; prolactinomas: 36. Varying doses of PBIr have been used, according to the various factors involved as well as the underlying diagnosis. For instance, 8,000 to 12,000 rads have been used for acromegaly, while a higher dose (12,000-15,000 rads) has been utilized for Cushing's, in order to obtain similar benefits in 83 percent of cases. Acromegalics had control of hGH to less than 10 ng/ml in 56 percent and improvement in another 27 percent. These results are usually apparent by 2 years. The risk of hypopituitarism in these patients was only 11 percent. There was less than 1 percent recurrence rate. In 65 cases of Cushing's disease and Nelson's syndrome, there was a 57 percent remission rate and a 26 percent improvement rate, for a similar percentage of over-all improvement as seen in acromegaly (83 percent). Their initial experience with prolactinomas employed lower doses (average of 4,000 rads in 30 cases). Analysis of prolactin levels in 11 cases showed a decrease of only 60 percent in 8 cases, so, si-

milar cases are now treated with 8,000 to 9,000 rads (9). After such a dose there was a transient decrease of prolactin in our patient (case 6) but prolactin activity recurred 14 months post PBIr. Being a rather young woman, the most identifiable and desirable goal is induction of spontaneous menses and hopefully, fertility. We are waiting at present for results with alphabromocriptine, if tolerated. At this writing, we have already had our first post-alpha-bromocriptine therapy uneventful delivery of a baby at the URH (10).

As mentioned elsewhere in relation to case 7, so far 8 patients have been given PBIr for tumor with suprasellar extension, utilizing a "double beam" technique in Boston. The previous 7 patients seem to have fared much better than did Case 6, who became pan-hypopituitary and blind. Of course, the inherent aggressiveness of the tumor must be taken into account. This is probably reflected by his most recent follow-up, again showing recurrent hyperprolactinemia, even after PBIr and 3 surgical interventions!

The excellent results of our first two cases, plus the over-all Boston experience (2, 6, 10, 11) demonstrate that PBIr can be a safe, convenient and effective means of therapy for pituitary functional tumors. Patient selection and stage of the disease process appear nevertheless, to play important roles in the outcome of such therapy, and a longer follow-up period than ours might be required for full therapeutic results. At any rate, it appears that close, judicious follow-up of each patient so treated is essential, for assessment of results and management of possible complications. Although the immediate costs could appear high, being able to administer the desired dose at one sitting involves the saving of personnel and the patient's time as well as equipment usage, which compen-

sates for its higher cost. The low ultimate incidence of hypopituitarism, and the preservation of ACTH reserve even among patients with Cushing's disease, would appear to be highly desirable ultimate goals of this therapeutic modality. The best results would appear to be most feasible among early, discrete pituitary tumors. Thus the importance of sound clinical appraisal and the new diagnostic tools in order to make earlier diagnoses.

Acknowledgments

The enthusiastic and valuable assistance of former and present Fellows in Endocrinology: Doctors Harry Jiménez, Gildred Colón, Myriam Allende, Alfred Mair, Ramón Ortiz Carrasquillo and Jorge de Jesús is gratefully acknowledged. Thanks are due also to various colleagues who referred to us some of the patients, including Dr. Edward O'Neill, and Dr. Ovidio Rodríguez Jr. and some rotating residents in Medicine, who participated in the evaluation and management of some of these patients. The excellent laboratory assistance of the Endocrinology and Radioimmunology Laboratory staff and the expert nursing carried out by the Clinical Research Center personnel are gratefully acknowledged. Ms. Julie Calero de Rivera and the personnel of the Audio-visual Communications Division of the Medical Sciences Campus are to be commended for their contribution in preparing the manuscript and the various figures of this work.

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related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily. **How Supplied:** Tablets—100 mg (white, scored), 50 mg (aqua) in bottles of 100, 1000 and 5000; 25 mg (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:

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Smith GR et al. *Psychosomatics* 15 138, 3rd quarter, 1974

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Tobin JM et al. *Geriatrics* 25(6):122, 1970

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Bernstein JG. *Clinical Psychopharmacology*
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Bernstein JG. *Management of Side Effects Related to Antipsychotic Drug Therapy* An Interview, 1978, p 12

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Warnings: Usage in Pregnancy: Safe use in pregnancy or in women likely to become pregnant has not been established, use only if benefit clearly justifies potential hazards. Infants should not be nursed during drug treatment.

Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity.

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL haloperidol may block its vasopressor activity and paradoxical further lowering of blood pressure may occur); (2) receiving anticoagulant medication since HALDOL haloperidol may lower the convulsive threshold; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving antiparkinson drugs, are administered concomitantly with HALDOL haloperidol. When HALDOL haloperidol is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL haloperidol. FD&C Yellow No. 5 (tartrazine) may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Adverse Reactions: CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug

may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn.

Persistent Tardive Dyskinesia: Although rarely reported with HALDOL haloperidol, tardive dyskinesia may appear during or after long-term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and sometimes appear irreversible; there is no known effective treatment and all antipsychotic agents should be discontinued. The syndrome may be masked by reinstitution of drug, increasing dosage, or switching to a different antipsychotic agent.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms.

Cardiovascular Effects: Tachycardia and hypotension. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication.

Liver Effects: Impaired liver function and/or jaundice reported. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair.

Endocrine Disorders: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia and hypoglycemia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Autonomic Reactions: Dry mouth, blurred vision, urinary retention and diaphoresis. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration.

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IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

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LA ETICA Y LAS PROFESIONES DE LA SALUD

La necesidad de conocer y practicar los conceptos aceptados de la ética en los campos de la salud debe ser inquietud viva y espontánea de cada profesional. Para los que no sienten esta actitud la motivación ha de ser el respeto o temor por la ley humana que protege a cada uno de nuestros ciudadanos contra la violación de sus derechos humanos y constitucionales.

La conducta ética correcta se basa en actitudes y conocimientos. Primero hay que tener la actitud favorable y ésta conduce a adquirir los conocimientos y ponerlos en práctica.

El concepto de lo que es ética puede ser estrecho y frío, o puede ser amplio, profundo y lleno de calor humano.

La ética debe ser honradez, integridad, justicia, amor al prójimo y decencia. Ha de manifestarse en forma de profundo respeto por los derechos y la dignidad de nuestros semejantes.

Se practica por medio de una vivencia, un estilo de vida y trabajo que en todo momento distinga entre el bien y el mal.

La practican muchos en parte y pocos enteramente. Esto es así porque somos humanos e imperfectos y, además, por desconocimiento pleno de sus diversos aspectos.

¿En qué consiste? El Juramento de Hipócrates es una definición que sirve de excelente punto de partida. Es el enfermo el eje alrededor del cual giran todos los elementos que componen la conducta ética del profesional de las ciencias de la salud. Comienza por un profundo respeto hacia el enfermo y sus familiares orientador de un trato cortés, compasivo, cuidadoso de preservar la confidencialidad de todo lo que ellos nos divulgan y de la dignidad de sus cuerpos y personalidades. Continúa con un trato similar hacia los compañeros profesionales, los estudiantes y todo personal que forme parte del equipo ya sea de una comunidad académica, de la oficina de un facultativo o de la compleja maquinaria de un gran centro médico.

¿Qué problemas hay con la ética? El principal problema es que muchos no la practican porque no la entienden y otros la conocen pero no quieren practicarla o se les olvida hacerlo. A veces, son los reglamentos del gobierno o de las compañías de seguros los que obligan a violarla.

La preservación de la confidencialidad de los datos vertidos en el expediente del enfermo es motivo de amplio debate: ¿deben éstos vaciarse en una computadora accesible a las distintas agencias o compañías de seguro? ¿Qué derecho tiene el paciente a que esto no se haga sin su permiso? ¿Quiénes deben tener acceso a esa información?

En un centro médico no hay que ir a las computadoras para identificar problemas relacionados con la violación de la confidencialidad. Son numerosas las personas que tienen acceso al expediente del enfermo. Cuando este es un desconocido y su caso es uno "de rutina" no suele haber problemas de divulgación, pero cuando es un conocido o se trata de un caso "interesante" el pro-

blema es serio. Un ejemplo recurrente es el del niño con genitales ambiguos; otro el del colega enfermo. Cuando un compañero de la profesión se enferma la celeridad con que se divulgan los más íntimos detalles de su dolencia es increíble, y nadie piensa que se están violando los principios de ética; no se ve como un paciente; es un compañero de trabajo; no tiene derecho a la confidencialidad de lo suyo; es como si se tratara de un familiar y todo el mundo se cree con derecho a conocer los detalles del caso.

¿Qué más abarca la ética de los profesionales de la salud? Sobre este tema se han escrito monografías, tratados y libros. El mismo puede entrar en rebuscados conceptos filosóficos y en situaciones difíciles, delicadas, en las que las opiniones personales o las creencias religiosas desempeñan un papel decisivo. Las decisiones relacionadas con situaciones de interpretaciones diversas, creencias personales, o con los problemas de vida o muerte que se presentan en las unidades de cuidado intensivo deben atenderse individualmente por comités especiales constituidos por personas idóneas. No se puede ofrecer una fórmula para atender automáticamente todos estos casos.

Pero la mayoría de los problemas de la ética son del diario vivir; la conducta a seguir ante los mismos está claramente establecida y la misma se rige por la aceptación por parte de nuestra sociedad de que los seres humanos tienen unos derechos los cuales deben respetarse y los cuales están regidos unas veces por la Ley Divina y otras por la humana; en la mayoría de los casos por ambas.

El profesional que practica la ética en sus funciones diarias demuestra evidencia de un profundo respeto por la vida y los derechos de sus pacientes; respeta y tolera las creencias religiosas, sociales, morales y políticas de éstos y no abusa de la necesidad que tiene el enfermo de sus servicios o de la confianza que ha depositado éste en su persona para coaccionarlo o imponerle sus creencias personales. El profesional ético mantiene la confidencialidad de la información recibida de sus pacientes. No se aprovecha de que éstos sean figuras conocidas o de alta jerarquía para darse importancia divulgando sus dolencias. Cuando presenta un caso en una sesión científica no divulga el nombre del enfermo. En las relaciones con el resto del personal de prestación de los servicios de la salud o con los estudiantes mantiene una actitud correcta, armoniosa, discreta y respetuosa. Delante de los enfermos no hace comentarios o gestos que puedan alarmarlos, confundirlos o causarles ansiedad a ellos o sus familiares. Si percibe conducta impropia en otro miembro del equipo no vacila en divulgarla, pero lo hace con la debida discreción, empleando los canales establecidos y dándole la oportunidad al posible culpable de aclarar su posición y explicar posibles malos entendidos, evitando así hacerle daño innecesariamente en caso de una equivocación.

El profesional ético reconoce el derecho del paciente de estar informado correctamente y después de haberle dado las explicaciones en forma clara y sencilla obtiene su consentimiento para los tratamientos médicos, los procedimientos, las intervenciones quirúrgicas o la investigación clínica. Cuando el profesional sirve como consultor debe estar consciente de los canales del cuidado del paciente y de sus limitaciones para imponer su criterio. Cuando dos consultores opinan diferentemente uno de los dos o cada uno de los dos tiene que estar equivocado. Estas son las situaciones en que el diálogo, el razonamiento científico y las juntas de expertos deben intervenir. Y esto ha de hacerse en un ambiente en el que se confronten ideas y no personas. Este mismo proceder debe regir en las relaciones entre los distintos miembros del equipo de prestación de los servicios de la salud. Resuélvanse las diferencias de ideas mediante el diálogo y estemos dispuestos a reconocer que todos somos humanos y nos equivocamos.

La divulgación al público por medio de la prensa, radio o televisión es parte importante de las funciones educativas del profesional de la salud, pero a la vez constituye un área de alto riesgo para caer fuera de lo ético. De hecho, es una de las funciones del buen reportero sacarle al entrevistado comentarios dramáticos, tajantes, si posible escandalosos; éstos son los que venden el periódico y atraen al radioescucha o televidente. La libertad de prensa y los medios de comunicación es uno de los derechos más codiciados de la democracia y no debe coartarse pero es un derecho que debe ejercerse responsablemente sin violar la confidencialidad de los enfermos, sin malicia, sin sensacionalismos, sin ofrecer curaciones radicales o secretas y sin agendas escondidas.

Los aspectos de la ética relacionados con anuncios, cobros, distribución de honorarios, criterios para servicios gratuitos, solicitud de pacientes, posesión de laboratorios, farmacias u hospitales tienen facetas variables de acuerdo con el tipo de profesión y las guías de sus colegios o asociaciones. Los médicos tradicionalmente no le han cobrado a los colegas, sus esposas, padres o hijos. Las excepciones habían sido los siquiátras, pero actualmente hay muchos otros médicos en los Estados Unidos que han suspendido la práctica de servicios gratuitos y otro gran número que han adquirido seguros médicos que le paguen a sus colegas para sentirse en mayor libertad de ocuparlos, ya que consideran la práctica de servicios gratuitos como un impedimento para obtener los servicios que necesitan.

Un aspecto de la ética que se interpreta en diversas formas tiene que ver con la responsabilidad del profesional hacia el enfermo. En la medida que sea posible es parte de un amplio concepto ético estar disponible en una emergencia, ser accesible, ser puntual y establecer un compromiso con el cuidado del paciente que incluya ofrecerle el seguimiento que sea necesario y no abandonarlo inesperadamente sin que éste tenga alternativas razonables.

El concepto de la ética ha de extenderse hasta la comunidad. Los profesionales de las ciencias de la salud deben estar atentos a los problemas que puedan afectar la salud de la comunidad e involucrarse en la medida que les sea posible en la solución de los mismos, particularmente, en aquéllos que son de su competencia.

La indiferencia ante los problemas de la comunidad tales como la contaminación del aire, fumar cigarrillos, la adicción a drogas, los accidentes, en fin de cuentas hace mucho más daño que la indiferencia no menos agravante ante un paciente aislado.

La enseñanza de la ética es de fundamental importancia para todos los que tienen la importante misión de formar los profesionales de la salud. Pero no se trata de un curso más en un currículo medular. Se trata de crear ambientes en los talleres de enseñanza que sirvan de modelo de práctica diaria de la ética profesional.

El mundo en que vivimos no nos permite darnos el lujo de ignorar los aspectos morales y éticos de nuestra conducta, pues los mismos han de determinar nuestra calidad de vida y posiblemente la supervivencia de la raza humana.

José E. Sifontes, MD

Comentario redactado a petición del Decano de la Escuela de Medicina, Dr. Pedro J. Santiago Borrero, y de la Decana de Estudios del Recinto Universitario de Ciencias Médicas, Dra. Lillian Haddock, para el "Regional Workshop in Humanities Education" auspiciado por la "National University Extension Association" y la Universidad de Puerto Rico, Hotel Holiday Inn Mayo 1980, San Juan, Puerto Rico.

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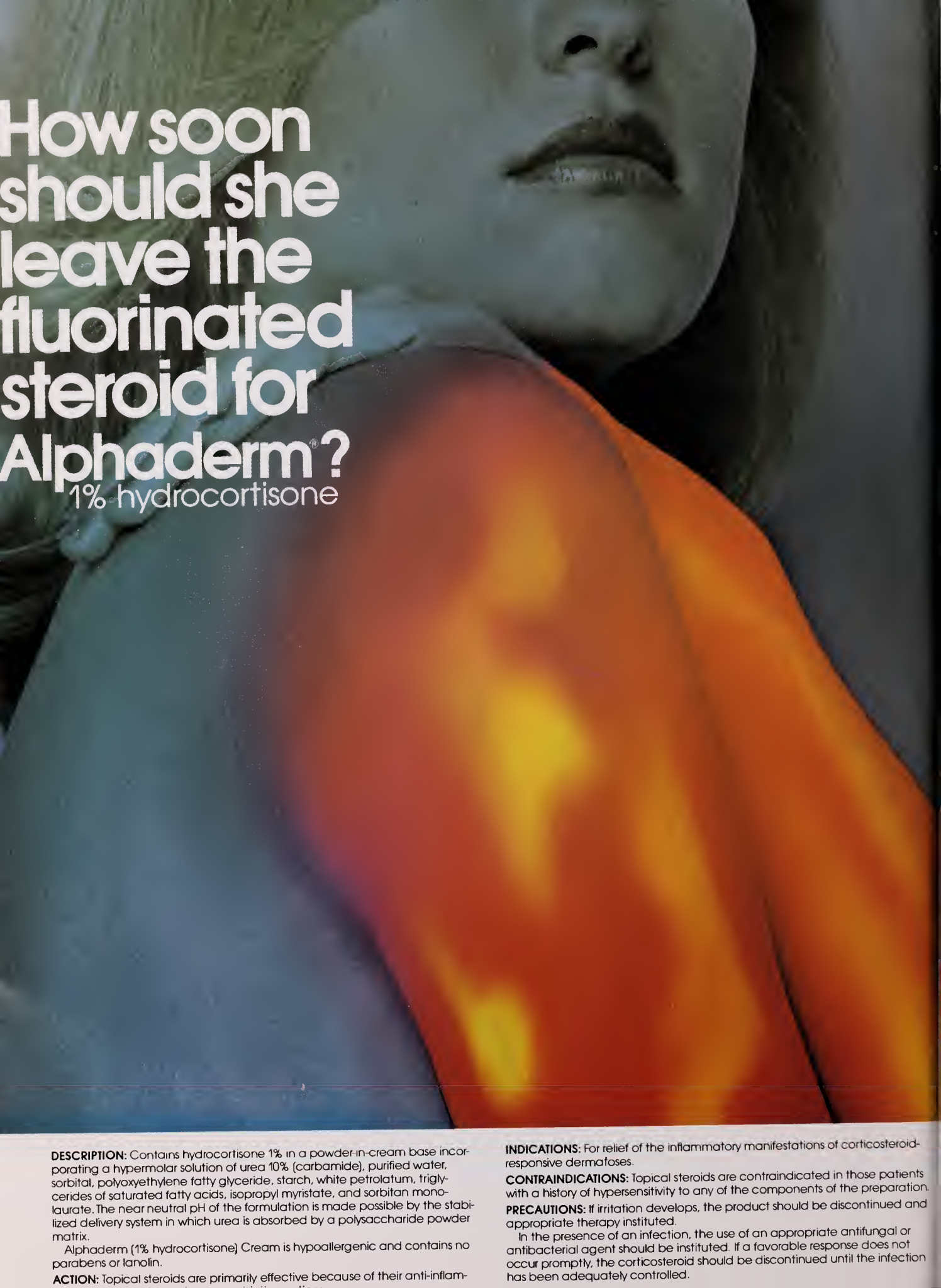
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**Broad-spectrum
coverage in mixed
helminthic infections**

Vermox[®] TABLETS
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Contraindications VERMOX is contraindicated in pregnant women (see: Pregnancy Precautions) and in persons who have shown hypersensitivity to the drug.

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PEDIATRIC USE: The drug has not been extensively studied in children under two years; therefore, in the treatment of children under two years the relative benefit/risk should be considered.

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** Mean egg reduction of VERMOX[®] in treating whipworm; egg reduction range of 70-99%. Data on file at Janssen Pharmaceutica Inc.

† Rollo, I.M.: Drugs used in the chemotherapy of helminthiasis, in Goodman, L.S.; and Gilman, A. (eds.): *The Pharmacological Basis of Therapeutics*, ed. 5. New York, Macmillan, 1975, p. 1034.

†† Miller, M.J.; Krupp, I.M.; Little, M.D.; Santos, C.: Mebendazole an effective anthelmintic for trichuriasis and enterobiasis. *JAMA* 230 (10): 1412-1414, Dec. 9, 1974.

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AVISO DE INTERES

La Junta Editora, consciente de su responsabilidad de hacer que el "Boletín" cumpla a cabalidad con su cometido de divulgar conocimientos médicos, elevar las normas de educación médica y al propio tiempo de llenar las necesidades de todos los compañeros médicos, ha acordado establecer una nueva Sección que se conocerá como "Sección de Preguntas".

Bajo esta nueva Sección, todos los compañeros tendrán la oportunidad de enviarnos preguntas médicas de casos difíciles o casos clínicos para opinión experta. Estas preguntas, con sus respuestas, serán publicadas en esta nueva Sección.

Las preguntas deberán ser enviadas a:

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Esperamos sus preguntas.

Juan M. Aranda, MD
Presidente
Junta Editora

EXERCISE FOR POST-CORONARY PATIENTS: ASSESSMENT OR INFREQUENT SUPERVISION

Kavanagh T, Shepart RJ - Arch Phys med. Rehabil. 61: 114-118, 1980.

Cuarenta y nueve pacientes los cuales asistían a un programa supervisado por un médico en base semanal por un año fueron transferidos a un régimen basado en la prescripción de actividad personal re-enforzado con visitas a sesiones de ejercicios supervisados por un médico cada ocho (8) semanas. Los datos se compararon con los de un grupo de 31 pacientes que seguían asistiendo a un programa regular. Diez (10) de los 49 pacientes experimentales demostraron deterioro de la adecuación respiratoria en el período de un año. De los 39 restantes 23, los cuales ya habían llegado a su límite máximo de entrenamiento, sostuvieron su condición mientras que 16 demostraron pequeñas ganancias continuas de fuerza aeróbica. Los programas poco frecuentemente supervisados demostraron ser seguros pero su efectividad terapéutica es dudosa. Considerando a los pacientes en el programa regular, las ganancias en fuerza aeróbica fueron pequeñas e inclusive hubo algún deterioro en el EKG al ejercicio durante el año de estudio.

(Sometido por Jesús A. Maldonado, MD)

EVALUATION AND PREDICTION OF BACK PAIN DURING MILITARY FIELD SERVICE

Nordgren B, Schele R, Liroth K; Scandinavian Journal of Rehabilitation Medicine. 12:1-8, 1980.

En un estudio en que 5,093 hombres comen-

zando entrenamiento militar, en edades entre 23-47 años (promedio 37), contestaron cuestionarios referentes a condiciones de espalda, cincuenta y tres por ciento indicaron haber tenido algún problema de espalda en su vida, 14 por ciento estuvieron afectados por problemas de espalda por un período mayor de un mes. Una sub-muestra de este grupo fue examinado usando un examen físico estandarizado. Aquellos individuos con trabajos civiles de menor exigencias físicas que la labor militar, en general presentaban menor fuerza isométrica de sus músculos abdominales y de espalda que otros sujetos. El examen físico fue más eficiente en separar aquellos sujetos que sufrieron dolor de espalda durante el entrenamiento que la información recopilada por medio de los cuestionarios referentes a problemas previos en los militares estudiados.

(Sometido por Frank W. López, MD)

PURINOGENIC IMMUNODEFICIENCY DISEASES: CLINICAL FEATURES AND MOLECULAR MECHANISM

Beverly S. Mitchel, MD, and William N. Kelley, MD - Ann Arbor, Michigan, Annals of Internal Medicine June 1980; 92: 826-831.

Deficiencies of two enzymes that catalyze sequential reactions in the purine catabolic pathway have been causally associated with immunodeficiency states. Adenosine deaminase (ADA) deficiency results in severe combined immunodeficiency disease, while purine nucleoside phosphorylase (PNP) deficiency results in an isolated T-cell defect. Recent work in this area has provided major new insights into the molecular pathology of these syndromes. Deoxyadenosine and deoxyguanosine, substrates that accumulate in

ADA and PNP deficiency, respectively, appear to be selectively phosphorylated by lymphoid cells to the corresponding deoxynucleoside triphosphate, resulting in inhibition of DNA synthesis in these cells. Both deoxynucleosides are far more toxic to cultured T lymphoblasts than to B lymphoblasts. Adenosine and deoxyadenoside may have additional lymphotoxic effects mediated by inhibition of essential methylation reactions. These observations help to explain the immunologic manifestations of ADA and PNP deficiency. Perhaps more important, they lay the foundation for the use of deoxynucleosides or enzyme inhibitors, or both, as selective immunosuppressive and chemotherapeutic agents.

(Submitted by Edwin Mejías, MD, VAH)

PLATLET FUNCTION STUDIES IN CORONARY DISEASE - EFFECT OF ASPIRIN AND TACHYCARDIA

Mehta J, Mehta P, Pepine C et al - American Journal of Cardiology 1980; 45: 945.

THROMBOXANE RELEASE DURING PACING INDUCED ANGINA PECTORIS

Lewy RI, Weiner L, Walinsky P et al - Circulation 1980; 61: 1165.

En el primero de estos artículos los autores evalúan el efecto de aspirina en el número y agregación de plaquetas en la cama vascular coronaria en pacientes con coronariopatía arteriosclerótica. En estos pacientes el número y agregación de plaquetas en el seno coronario es menor que en la aorta indicando una posible activación de las plaquetas en la red coronaria. Al inducir taquicardia la agregación de plaquetas disminuye aún más en el seno coronario. La administración de aspirina produjo un aumento en el número y agregación de plaquetas en el seno coronario y revirtió los cambios inducidos

por la taquicardia.

En el segundo artículo los autores miden los niveles de tromboxano A_2 en el seno coronario y en una arteria durante taquicardia en pacientes con coronariopatía arteriosclerótica. Al producirse isquemia micocárdica (comprobada por lactatos en el seno coronario) se notó un aumento en el tromboxano arterial y aún mayor en el tromboxano en el seno coronario.

Estos artículos nos indican que las plaquetas juegan un papel importantísimo en la enfermedad coronaria, no por el puro factor mecánico sino por su influencia hormonal. Es muy posible que el mecanismo del espasmo coronario, que aparentemente es uno de los factores claves en el cuadro de infarto o angina inestable, sea mediado de una manera similar.

(Sometido por Guillermo Cintrón, MD, VAH)

MARROW APLASIA FOLLOWING TOPICAL APPLICATION OF CHLORAMPHENICOL EYE OINTMENT

Abrams, S. M. et al - Arch. Intern. Med. 140: 576-578, 1980.

La anemia aplásica inducida por cloranfenicol está bien descrita en la literatura médica. Cloranfenicol puede producir dos efectos diferentes en la médula ósea. La forma más común se caracteriza por una supresión de la médula que es reversible y asociada a la dosis. La segunda forma, que es rara, es la aplasia irreversible de la médula, afectando las 3 líneas celulares y resultando en muerte. El riesgo de desarrollar anemia aplásica fatal es 13 veces más alto en los individuos tratados con cloranfenicol oral que en la población no tratada. La toxicidad parenteral no está muy claramente definida. En este artículo se describe un hombre de 33 años que desarrolló anemia aplásica después de recibir unguento oftálmico de cloranfenicol, polymyxina B, el cual usó

intermitentemente por 4 meses. El cuadro de pencytopenia surgió y el paciente sucumbió a la enfermedad en 3 meses. Se han reportado varios casos (2) de anemia aplástica después del uso de gotas oftálmicas con cloranfenicol, éste es el primer caso con unguento.

Es importante recordar este caso y evitar mientras sea factible el uso de este compuesto en infecciones benignas o en infecciones que pueda utilizarse otro agente menos tóxico.

(Sometido por Carlos H. Ramírez Ronda, MD, VAH)

MEDI QUIZ ON RENAL MEDICINE

1. The effects of severe hyponatremia (serum sodium < 125 mEq/L) on the central nervous system:
 - A. Correlate well with the plasma sodium concentration.
1. The effects of severe hyponatremia (serum sodium < 125 mEq/L) on the central nervous system:
 - A. Correlate well with the plasma sodium concentration.
 - B. Include lethargy, confusion, stupor, coma, and seizures.
 - C. Should be treated with isotonic saline.
 - D. May be associated with decreased brain water and increase in brain electrolytes.
2. Hormones important in the non-osmolar regulation of renal water excretion include all of the following *except*:
 - A. Prostaglandins.
 - B. Catecholamines.
 - C. Adrenocortical hormones.
 - D. Thyroid hormone.
 - E. Growth hormone.
3. Which of the following is/are true concerning SIADH (Syndrome of Inappropriate Secretion of Antidiuretic Hormone) as a cause of hyponatremia?
 - A. Hypertonic saline, demeclocycline, and fluid restriction may all be used in the management of this syndrome.
 - B. Hypouricemia is an associated finding.
 - C. The diagnosis is established by showing urine hypertonic to plasma in the absence of hypovolemia and edematous states, and with normal adrenal, renal, and thyroid functions.
 - D. It is associated with the use of anti-neoplastic agents, tricyclic antidepressants, chlorpropamide, clofibrate, and carbamazepine.
 - E. All of the above.
4. In screening for renal vascular hypertension, which of the following has *not* been found effective, when used with the others, in detecting renal artery stenosis?
 - A. Rapid sequence IVP.
 - B. Saralasin infusion.
 - C. Upright resting plasma renin.
 - D. Presence of a systolic and diastolic abdominal bruit.
5. An increased anion gap [sodium - (chloride + bicarbonate) > 12 mEq/L] is associated with all of the following *except*:
 - A. Keto-acidosis.
 - B. Paraldehyde poisoning.
 - C. Renal tubular acidosis.
 - D. Uremic acidosis.
 - E. Ethylene glycol ingestion.
6. In evaluating a patient with rapid deterioration of renal function, which of the following suggests a diagnosis of acute tubular necrosis?
 - A. Urine osmolality less than 350 mOsm/kg.

- B. Urine sodium concentration less than 20 mEq/L.
C. Urine-to-plasma creatinine ratio > 40.
7. Acute renal failure due to radio-contrast agents has been associated with:
- A. A variety of x-ray procedures, including oral cholecystography, intravenous urography, and coronary arteriography.
B. Diabetes mellitus.
C. Dehydration.
D. Pre-existing renal disease.
E. All of the above.
8. A patient with chronic atrial fibrillation presents with right flank pain. Which of the following does *not* support the diagnosis of renal artery embolus?
- A. Proteinuria.
B. Red blood cell casts.
C. Elevated serum lactic dehydrogenase.
D. Fever and leukocytosis.
E. Hematuria.
9. A patient presents with mild chronic renal failure, minimal proteinuria, urinary sediment without casts, and hyperchloremic metabolic acidosis. The differential diagnosis includes all of the following *except*:
- A. Analgesic abuse.
B. Hypercalcemia.
C. Obstruction.
D. Chronic glomerulonephritis.
E. Sickle cell disease.
10. Match each of the following drugs with the type of renal problem it is most likely to cause:
- A. Gentamicin.
B. Methysergide.
C. Ritalin®.
D. Oxacillin.
E. Heroin.
F. Percodan®
1. Obstructive uropathy.
2. Chronic interstitial nephritis.
3. Acute tubular necrosis.
4. Nephrotic syndrome.
5. Renal arterial obstruction.
6. Acute interstitial nephritis.
11. Which of the following support(s) a diagnosis of primary hyperaldosteronism?
- A. Serum K⁺ less than 4.0 mEq/L.
B. Normal plasma renin after salt and volume depletion.
C. Serum Na⁺ greater than 140 mEq/L.
D. Normal plasma and urinary aldosterone secretion after sodium loading.
E. All of the above.
12. Chronic renal failure is associated with all of the following endocrinologic abnormalities *except*:
- A. Insulin resistance.
B. Excessive secretion of parathyroid hormone.
C. Hypothyroidism.
D. Elevated gastrin levels.
E. Elevated growth hormone levels.
13. Which of the following is *false* concerning hypertension in dialysis patients?
- A. It is always volume dependent.
B. It is sometimes associated with elevated renin secretion.
C. It may respond to increased dialysis.
D. It can be successfully treated with vasodilators (minoxidil).
E. It may respond to nephrectomy.

14. Membranous nephropathy is:

- A. Sometimes steroid responsive.
- B. Associated with neoplasia.
- C. More common in adults.
- D. Associated with systemic lupus erythematosus.
- E. All of the above.

15. Non-oliguric acute renal failure (defined as acute reduction of renal function with a daily urine volume greater than 600

cc):

- A. Has a poorer prognosis than oliguric acute renal failure.
- B. May result from using Lasix® in oliguric acute renal failure.
- C. Is infrequently associated with aminoglycoside antibiotics.
- D. Has different urinary diagnostic indices than oliguric acute renal failure.

(REPRINTED BY PERMISSION FROM HOSPITAL PHYSICIAN 4: 56-58, 1980)

(Contestaciones en página 360)



ASOCIACION MEDICA DE PUERTO RICO

SEPRE ESTE FECHA: NOV. 25 - 29, 1980

ASAMBLEA ANUAL

CENTRO DE CONVENCIONES

Tenuate® ^{TV}

(diethylpropion hydrochloride NF)

Tenuate Dospan®

(diethylpropion hydrochloride NF) controlled-release

AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

INDICATION Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.

CONTRAINDICATIONS Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).

WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle, the patient should therefore be cautioned accordingly. *Drug Dependence:* Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression, changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy:* Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children:* Tenuate is not recommended for use in children under 12 years of age.

PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.

ADVERSE REACTIONS: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System:* Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache, rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic:* Urticaria, rash, ecchymosis, erythema. *Endocrine:* Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System:* Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous:* A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.

DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride) One 25 mg tablet three times daily, one hour before meals, and in the evening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release. One 75 mg tablet daily, swallowed whole, in the morning. Tenuate is not recommended for use in children under 12 years of age.

OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phenolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product information as of April, 1976

MERRELL-NATIONAL LABORATORIES Inc.

Cayey, Puerto Rico 00633

Direct Medical Inquiries to

MERRELL-NATIONAL LABORATORIES

Division of Richardson-Merrell Inc.

Cincinnati, Ohio 45215, U.S.A.

Licensors of Merrell®

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Merrell

**Overweight may not always be simple...
complications can develop*.**

Complicated or not...

Tenuate[®] Dospan[®] ^{IV} **(diethylpropion hydrochloride NF)** **75 mg. controlled-release tablets**

A useful short-term adjunct in an indicated weight loss program.

Overweight patients in certain diagnostic categories often require strict appetite control and a successful program of weight reduction may tend to diminish the incidence or severity of the complications in some patients. Diethylpropion hydrochloride has been reported useful in such patients and while it is not suggested that Tenuate itself in any way reduces the complications of overweight, it may have a useful place as a short-term adjunct in a prescribed dietary regimen. **Tenuate should not be administered to patients with severe hypertension; see additional Warnings and Precautions on the opposite page.**

In uncomplicated overweight.

Many patients, on the other hand, present with excess fat but no disease. While this condition is often termed uncomplicated obesity, complications of both a social and a psychologic nature may be distressingly real for the patients. In these cases, a short-term regimen of Tenuate can help reinforce your dietary counsel during the important early weeks of an indicated weight loss program.

Clinical effectiveness.

The anorectic effectiveness of diethylpropion hydrochloride is well documented. No less than 16 separate double-blind, placebo-controlled studies attest to its usefulness in daily practice.¹ And the unique chemistry of Tenuate provides "...anorectic potency with minimal overt central nervous system or cardiovascular stimulation."² Compared with the amphetamines, diethylpropion has minimal potential for abuse.

**Tenuate—it makes sense.
And it's responsible medicine.**

*Studies have shown that obesity is associated with an increased incidence of hypertension, symptomatic heart disease, adult-onset diabetes, and other diseases.

Merrell



For prescribing information see opposite page

In G.I. therapy



Adjunctive Librax[®]

Each capsule contains
5 mg chlordiazepoxide HCl
and 2.5 mg clidinium Br

antianxiety/antisecretory/antispasmodic

for adjunctive therapy of duodenal ulcer* and irritable bowel syndrome*

Librax[®]

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma, prostatic hypertrophy, benign bladder neck obstruction, hypersensitivity to chlordiazepoxide HCl and/or clidinium Bromide.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium[®] (chlordiazepoxide HCl/Roche) to known addicts.

tion-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially, increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression: suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug

and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated, avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction, changes in EEG patterns may appear during and after treatment, blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, i.e., dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

ROCHE

Roche Products, Inc.
Manati, Puerto Rico 00701

ELECTROCARDIOGRAM OF THE MONTH

The electrocardiogram (ECG) and Frank vectorcardiogram (VCG) illustrated in Figures 1 and 2 are those of a 25-year old nurse with nonspecific chest pains. The physical examination and chest roentgenogram were normal.

These data are compatible with which of the following diagnoses (one or more than one):

1. Normal.
2. Old inferior myocardial infarction (scar).
3. Left anterior hemiblock (block of the superior fascicle of the left bundle branch).
4. Both diagnoses 2 and 3.
5. None of the above.
6. What is your clinical diagnosis?
7. Further information is needed.
8. What other data is required?

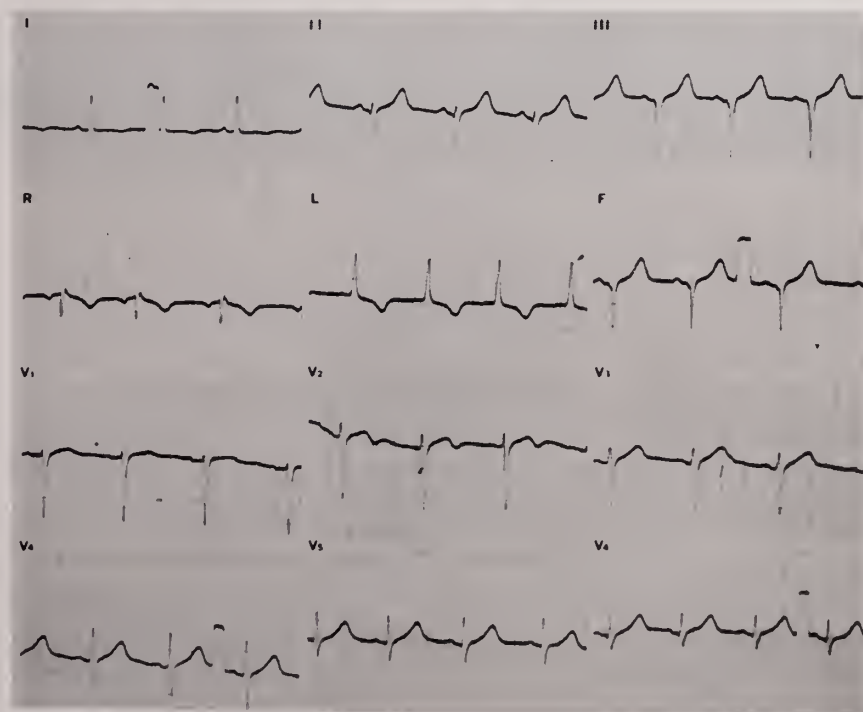


FIGURE 1

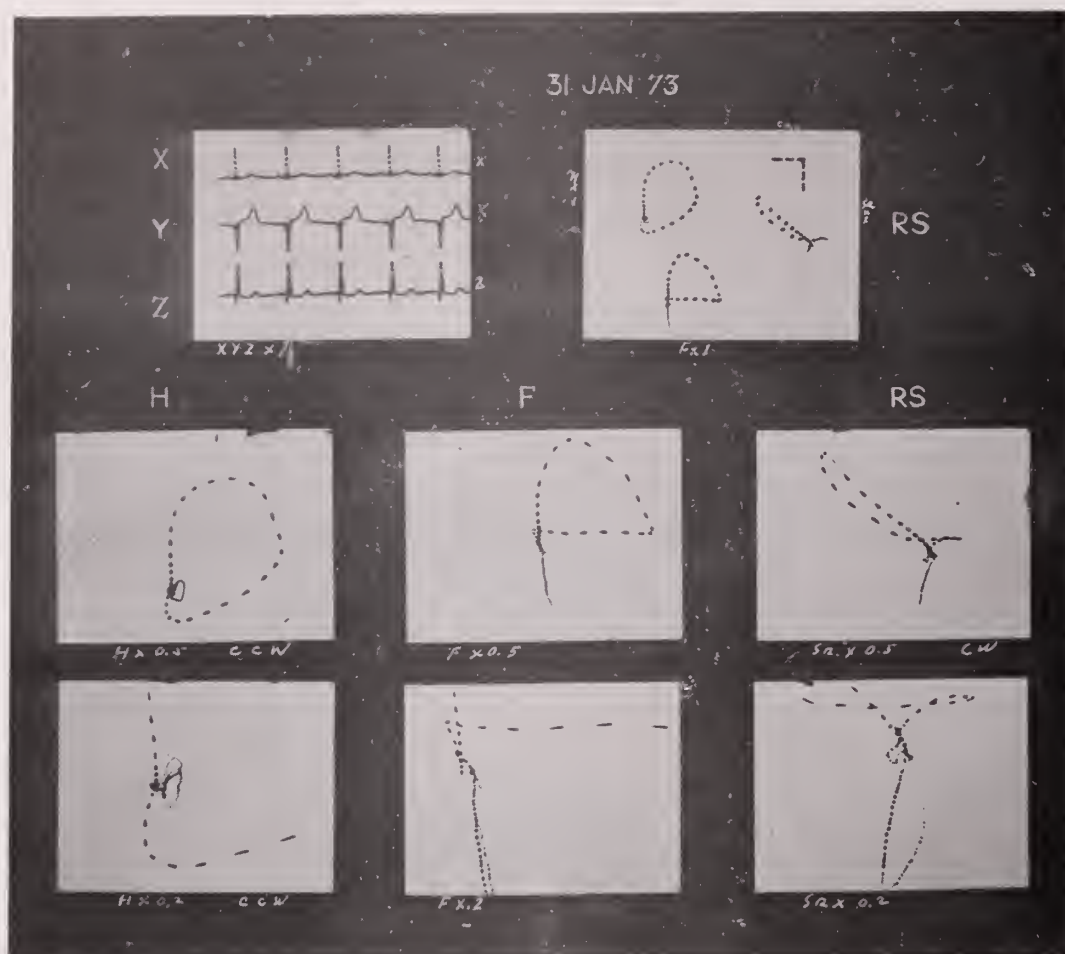


FIGURE 2

Answer

The P-R interval measures 0.14 S and the QRS 0.08- .09 S. The QRS axis is -45 to -50 degrees. The T waves are diphasic in leads I and V_2 and inverted in aVL. There are no q's in leads I nor aVL but small q waves appear in II and slurred QS complexes in leads III and aVF. Lead Y is a QS complex. The VCG depicts superior frontal (F) and right sagittal loops, predominantly clockwise initially (with the initial F vector superior and rightward), later rotating counterclockwise in the F plane. No initial inferior vectors are evident.

These traces suggest both left anterior hemiblock (LAH) and inferior scar because of: the relatively large R waves in leads I and aVL, the relatively large QS complexes in III and aVF, the slur or ledge within the initial downward QS deflection, a qrS in lead II, absence of terminal R in III, absent q in I and small q in lead II, and the superior, leftward posterior QRS loop with a clockwise superior efferent limb (the inferior infarction) and a counterclockwise, superior delayed afferent loop (the LAH).

The cardiac catheterization and left ventricular angiogram were normal, but apparently ventricular fibrillation occurred during the procedure; the coronary arteries were small but within normal limits.

The causes of Q waves other than myocardial infarction (MI) - coronary embolus, ventricular aneurysm- are legion (pseudoinfarction): normal, positional (long chest, asthenic body build, stocky or obese with high diaphragm, atypical heart position), chest deformities, malposition of electrodes, vagotonia as in the athletic heart, cardiomyopathies, particularly hypertrophic obstructive (3) cardiomyopathy (HOCM), due to septal hypertrophy or fibrosis and/or abnormal septal and left ventricular (LV) wall activation, amyloid heart disease, Chagas' disease, neuromuscular diseases (Duchenne muscular dystrophy, Friedrich's ataxia), mitral valve prolapse (MVP), sarcoid heart disease, right and left ventricular hypertrophy with LV diastolic overload, right atrial enlargement, left bundle branch block, LAH, left posterior hemiblock, a negative delta wave of the WPW syndrome, acute pulmonary embolus, chronic obstructive lung disease with cor pulmonale, pneumothorax, aortic stenosis and regurgitation, congenital heart disease and anomalies of the coronary arteries (corrected transposition of great arteries, tricuspid atresia, Ebstein's anomaly, atrial septal defect, PDA, malposition, Bland-White-Garland syndrome), CNS diseases (especially intracranial hemorrhage), cardiac trauma, electric shock, radiation, collagen diseases (scleroderma, lupus erythematosus, periarteritis nodosa, Takayasu's), primary and metastatic tumors of heart, leukemic infiltrates, constrictive pericarditis (myocardial fibrosis), acute myocarditis (viral, infectious mononucleosis, rabies, typhoid fever, tetanus, trichinosis, pheochromocytoma), glycogen storage and Fabry's diseases, Sheehan's syndrome and polycythemia vera; as well as transitory Q waves of ischemia, Prinzmetal's angina, exercise testing, atrial pacing, tachycardia- rate dependent right precordial Q's (septal focal block), electrical silence, acute pancreatitis, heart surgery, selective coronary arteriography, asthma, shock and severe metabolic stress, hepatic abscess, phosphorus poisoning, uremia and hyperkalemia, etc.

Presently there is no definitive clinical diagnosis on this (4) patient. One must examine: MI from coronary artery disease (CAD), small vessel CAD, coronary artery spasm, a WPW syndrome variant, a cardiomyopathy (the Q's due to multiple areas of necrosis and fibrosis scattered throughout the septum and LV), and recently special credence to MVP. Young women have been reported with MI and angina in the presence of normal coronary arteriograms. Cardiomyopathies may present Q waves, normal arteriograms, a delta-like wave (WPW) and mitral ballooning (HOCM). Coronary artery spasm can induce MI, ventricular tachycardia and fibrillation. MVP is recognized widely in young females ("click chicks") with angina-like chest pain, and it seems to be associated with coronary spasm. MVP is associated with CAD but CAD is not more frequent than in the general population. However, MVP is regarded by many authorities as a cardiomyopathy manifesting abnormal systolic contractions of various types. It can cause serious arrhythmias. Convincingly, a number of cases of MI patterns (Q's) by ECG and VCG have been described with MVP and normal coronary arteries; or with those of a corkscrew pattern, short main left artery, anomalous origin of the right or circumflex arteries, congenital absence of the circumflex, and a single obtuse marginal branch arising from the circumflex but an absent or hypoplastic AV groove branch.

An echocardiogram, exercise stress testing, radioisotope studies and perhaps recatheterization

(with provocative testing) are merited in a quest for a sure diagnosis.

An axion with ratiocination is: Q waves are not synonymous with MI or CAD!

The great Frank Wilson wrote on electrocardiography, "and there are comparatively few people who are not in greater danger of having their peace and happiness destroyed by an erroneous diagnosis of cardiac abnormality based on a faulty interpretation of an electrocardiogram, than of being injured or killed by an atomic bomb."

Charles D. Johnson, MD
UPR School of Medicine
Dept. of Medicine

Acknowledgment

To Drs. J. E. López and B. Betancourt for their roles in the management of this patient.

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ARTERIOVENOUS MALFORMATION/BRAIN SCAN

Julio V. Rivera, MD, FACP and René
Cardona Campos, MD, FACS

Case Summary

A 55-year old male was admitted on February 15, 1980 with a history of transient loss of consciousness followed by left hemiparesis and aphasia which occurred in December, 1979. He recovered consciousness rapidly and the other symptoms improved by the time of admission. In 1977 the patient had aphasia which lasted about one hour.

Diabetes mellitus and micronodular cirrhosis had been diagnosed several years before.

At the time of admission the patient was described as alert and he did not have nuchal rigidity. Neurological examination showed minimal signs of left hemiparesis.

Brain scan, including dynamic phase, showed a highly vascular right parietal region adjacent to the sagittal sinus with some extension across midline. It was less obvious in the delayed views (Figs. 1, 2, 3). A diagnosis of arteriovenous malformation was favored.

Computerized axial tomogram of the brain showed a localized high density lesion in the same location as seen on the brain scan, without definite enhancement upon the injection of contrast material. These findings were interpreted as due to neoplasm.

Carotid arteriogram detected a hypervascular parietal mass with multiple "tumor vessels" and large relatively late filling venous drainage. Diagnoses of malignant glioma or meningioma were suggested.

Craniotomy on March 8, 1980 revealed a large parasagittal arteriovenous malformation in the right parietal region.

Comments

Arteriovenous malformations (AVM) of the cerebral vessels are congenital anomalies which not infrequently first become clinically manifest in adult life. Only about half of the patients are symptomatic before the age of 30 (1). These anomalies represent less than 4 percent of all intracranial "mass" lesions. Symptoms may occur as a result of hemorrhage, thrombosis or mass effect. These may include headaches, seizures or other focal manifestations which will vary according to their localization.

Cerebral dynamic scintigraphy is very effective in the demonstration of AVM (1, 2, 3). They are identified, as in the present case, as highly vascular focal lesions during the arterial phase which may fade rapidly during venous drainage. Premature venous drainage may be evident by observation of the emergence of radioactivity in the dural sinuses

From the Surgical and Nuclear Medicine Services, Veterans Administration Medical and Regional Office Center, San Juan and the University of Puerto Rico School of Medicine.

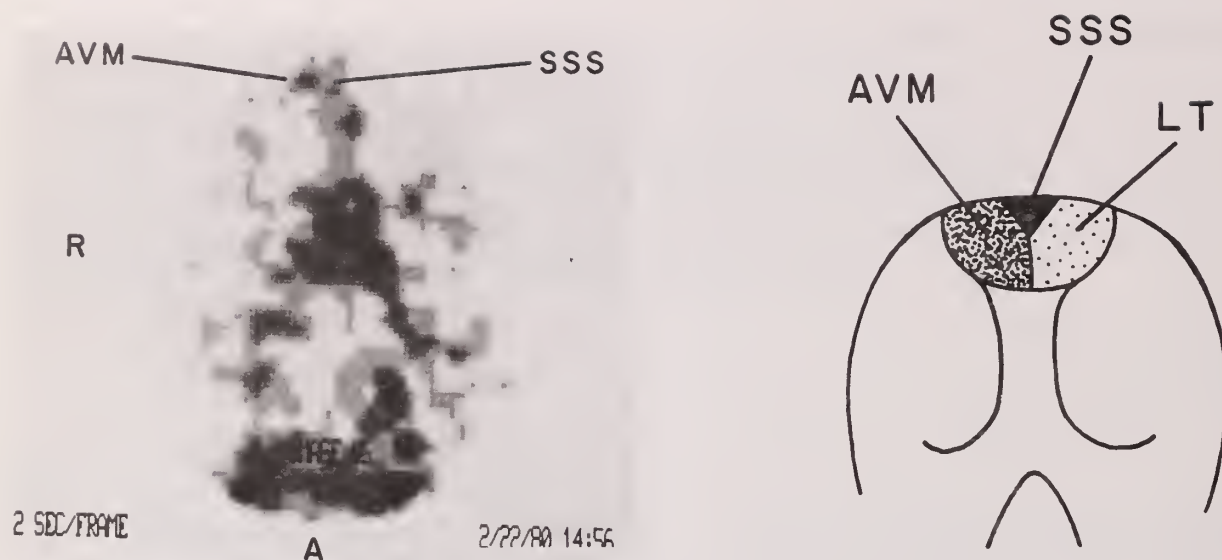


Figure 1: (A) Computer processed anterior view of radionuclide "angiogram" shows increased flow to region adjacent and to the right of the sagittal venous sinus. (B) Diagram of same image also indicates regions chosen for radioactivity curves. SSS = superior sagittal sinus. AVM = arteriovenous malformation (curve - R). LT = corresponding area in the left hemisphere (curve -LT).

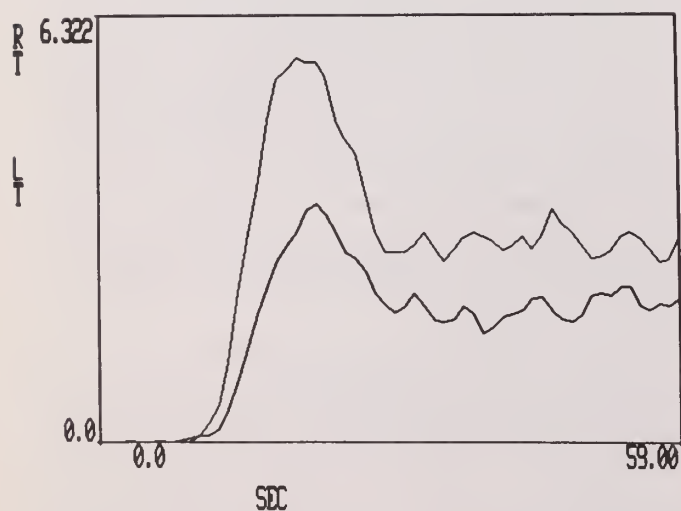


Figure 2: Activity curves of regions of interest on each side of the sagittal sinus show an earlier and taller peak and a more rapid downslope in the AVM than in the opposite side.

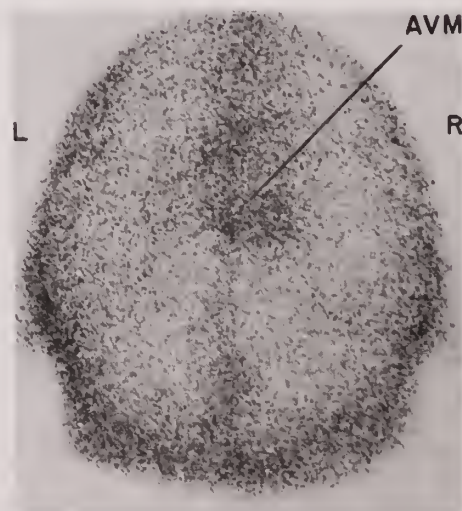


Figure 3: Vertex view of the brain demonstrates localization of the AVM adjacent to the sagittal sinus.

in serial images. Computer quantitation of levels of radioactivity in selected areas of interest is extremely useful in the objective documentation of these changes. In contrast to most highly vascular brain tumors such as high grade gliomas and meningiomas, AVM are much less apparent in delayed views. This important clue in the differential diagnosis was helpful in this case.

Computerized transmission tomography is less effective than radionuclide scintigraphy in the detection of these anomalies unless contrast enhancement is used (2, 3). Even with the addition of the latter, in the present case, the true nature of the lesion was misjudged. Because of its known morbidity, contrast angiography is not advisable as an initial

screening or diagnostic procedure and its usefulness lies in the detailed delineation of vascular channels which is necessary in the planning of a surgical procedure.

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QuinammTM

AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

INDICATIONS: For the prevention and treatment of nocturnal recumbency leg muscle cramps, including those associated with arthritis, diabetes, varicose veins, thrombophlebitis, arteriosclerosis, and static foot deformities.

CONTRAINDICATIONS: Because of the quinine content, Quinamm is contraindicated in women of childbearing potential, in pregnancy, in patients with known quinine sensitivity, and in patients with glucose-6-phosphate dehydrogenase deficiency. Hemolysis (with the potential for hemolytic anemia) has been associated with a G-6-PD deficiency in patients taking quinine.

PRECAUTIONS: Thrombocytopenic purpura may follow the administration of quinine in highly sensitive patients. Recovery will follow withdrawal of the medication. Cinchona alkaloids, including quinine, have the potential to depress the hepatic enzyme system that synthesizes the vitamin K-dependent factors. The resulting hypoprothrombinemic effect may enhance the action of warfarin and other oral anticoagulants.

ADVERSE REACTIONS: Aminophylline may produce intestinal cramps in some instances, and quinine may produce symptoms of cinchonism, such as tinnitus, dizziness, and gastrointestinal disturbance. If ringing in the ears, deafness, skin rash, or visual disturbances occur, the drug should be discontinued.

DOSAGE AND ADMINISTRATION:

1 tablet upon retiring. When necessary, 1 additional tablet may be taken following the evening meal

Product Information as of September, 1977

U.S. Patent 2,985,558

Merrell

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for Knotts in the night



QuinammTM

each tablet contains quinine sulfate 260 mg., aminophylline 195 mg.

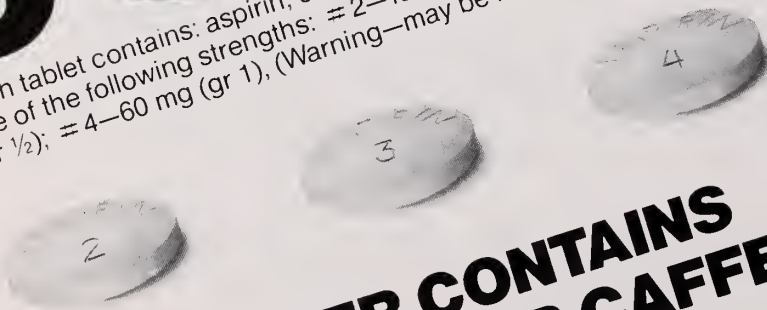
specific therapy for painful night leg cramps

Nocturnal recumbency leg muscle cramping is frequently an unwelcome bedfellow for many patients—especially those with arthritis, diabetes or peripheral vascular disease ... consider Quinamm ... simple, convenient dosage—usually just one tablet at bedtime ... can provide restful, welcome sleep without night leg cramps.

See opposite page for prescribing information.

~~EMPIRIN[®]~~ ~~COMPOUND~~ ~~CODEINE~~ IS NOW ~~EMPIRIN[®]~~ ~~CODEINE~~

Each tablet contains: aspirin, 325 mg; plus codeine phosphate in one of the following strengths: $\approx 2-15$ mg (gr $\frac{1}{4}$); $\approx 3-30$ mg (gr $\frac{1}{2}$); $\approx 4-60$ mg (gr 1), (Warning—may be habit-forming)

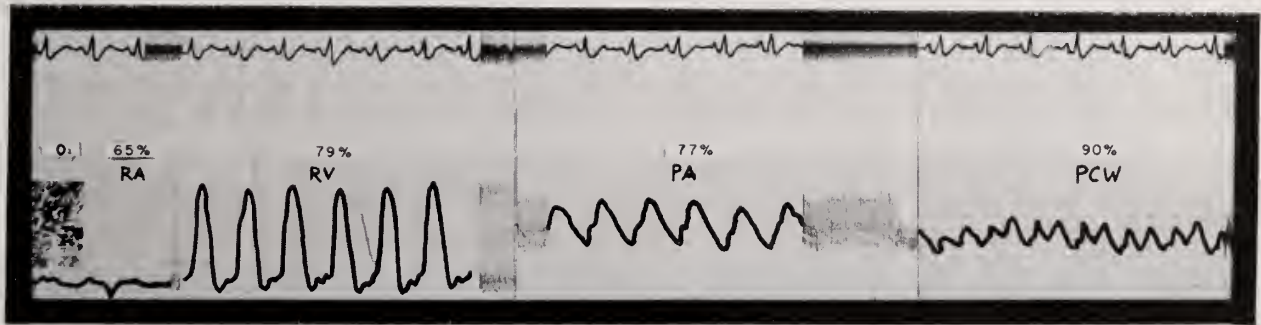


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GRAPHICS



A. R. A. es un paciente varón de 67 años que se admite con un infarto cardíaco agudo. En el 5to. día desarrolla edema de pulmón y se le descubre un nuevo soplo holosistólico en el borde esternal izquierdo. La gráfica adjunta demuestra el electrocardiograma en la línea superior y presiones intracavitarias de las cámaras cardíacas derechas en la línea inferior. La saturación de la hemoglobina en las diferentes cámaras está expresada en por ciento.

El diagnóstico es:

- 1) rotura de músculo papilar
- 2) rotura de septo interventricular
- 3) choque cardiogénico

CONTESTACION (2)

El cuadro clínico de un paciente con su primer infarto cardíaco que desarrolla un nuevo soplo con el cuadro de edema agudo

de pulmón sugiere el diagnóstico de rotura de septo interventricular o músculo papilar.

La localización del soplo y la intensidad del mismo puede ayudar en el diagnóstico diferencial. El diagnóstico se documenta por cateterismo cardíaco que demuestra un aumento en la oxigenación sanguínea en el ventrículo derecho en casos de rotura interventricular (como en la gráfica arriba). En casos de rotura de músculo papilar se demuestra un aumento en la onda V en la posición en cuña pulmonar. Rotura de músculo papilar es casi exclusiva de infartos inferiores, rotura de septo interventricular se ve en infarto anterior o inferior. El manejo médico está enfocado a mejorar la oxigenación sistémica y disminuir la edema pulmonar mediante diuréticos, vasodilatadores y agentes inotrópicos.

En casos donde el paciente no demuestra mejoría en 2-4 horas se debe considerar cirugía de emergencia.

Guillermo Cintrón, MD

AMA NEWS:

WALKING IS GOOD EXERCISE

CHICAGO — The physical fitness boom of recent years has sent millions of Americans to the jogging paths, swimming pools and health club gyms. But the majority are still living their usual sedentary lives while watching the fitness buffs with amused contempt.

Physical fitness programs have had no success in inducing the majority of the population to be physically active, says Yehuda Shoenfeld, MD, of Tel-Aviv University Medical School, Israel.

Writing in the May 23/30 Journal of the American Medical Association, Dr. Shoenfeld points out that jogging, although efficient in improving heart and lung capacity, is unsuitable for large population groups. Moreover, it has been found to cause some harmful side effects.

Almost everyone can walk, but is walking really enough exercise to improve physical condition appreciably?

Yes, says Dr. Shoenfeld, reporting on experience in measuring exercise capacity of 44 young men in a research training program. Some of the men hiked for 30 minutes each day at a speed of three miles per hour, carrying a small seven-pound back pack. Several of the subjects walked for four to six weeks with the same load, and some increased the load to 14 pounds.

In all groups, exercise capacity showed significant increase, but was most pronounced in the last group, Dr. Shoenfeld says.

This study shows that it is possible to improve substantially physical fitness in three weeks by walking daily with a light back-pack load, he concludes.

Walking can easily be adapted as a way of life; everyone can use a briefcase or shopping bag ra-

ther than a back pack. By increasing the speed, distance and pack load, individuals can attain a fairly high degree of physical conditioning, he says.

STUDY CONFIRMS EFFECTIVENESS OF ENZYME TREATMENT FOR BACK PAIN

CHICAGO — Followup studies of from three to six years show clearly that chymopapain — the controversial enzyme treatment for slipped disks and severe back pain — works for a large majority of sufferers.

Chymopapain was used in lieu of surgery to relieve the pain of slipped disk for some years, but fell into disfavor and was prohibited by the Food and Drug Administration in 1975. It is an enzyme that is injected into the spinal column to cause disintegration of the protruding disk.

Manucher J. Javid, MD, neurosurgeon at the University of Wisconsin, Madison, reports in the current issue of the Journal of the American Medical Association, on experience with 124 patients who were treated with chymopapain prior to FDA's withdrawal of the drug. One year after the injection, 90 patients (72.6 per cent) experienced major improvement. 21 (16.9 per cent) had slight improvement, and 13 (10.5 per cent) had no improvement.

Of those patients who had no previous back surgery, 77 patients (81 per cent) had marked improvement, 13 (13.7 per cent) had slight improvement, and five (5.3 per cent) had no improvement Dr. Javid says.

Three to six-year followups were obtained by questionnaire. Of the 114 patients responding, 83 patients (72.8 per cent) had marked improvement, and 75 (83.3 per cent) of those with no previous surgery had major improvement.

Since all patients met the criteria for back

surgery, favorable results from the enzyme injection spared most the trauma of surgery, Dr. Javid points out.

"These results indicate that chemonucleolysis (technical name for the enzyme treatment) can and should be considered an advantageous alternative to surgery in appropriately selected patients," he says. Surgery should be reserved only for those few who fail to respond to enzyme treatment, he states.

The enzyme has been used extensively by 75 physicians in the United States and Canada in more than 17,000 patients and has been widely reported to be effective. However, it still is banned in the United States, and U. S. nationals wishing chymopapain treatment must go to Canada, where it is legal and in regular use.

JOGGERS CAUTIONED AGAINST HEAT STROKE

CHICAGO — North America's 30 million joggers were cautioned this week as summer approaches to beware of heat stroke.

Runners should pay close attention to the well-known rules for training, heat acclimatization, taking plenty of fluids, and diet, says a communication in the May 16 *Journal of the American Medical Association*.

In scheduled long distance runs it is important for the first aid center to have facilities for rapid cooling of all heat injury patients without delay, says John R. Sutton, MD, of McMaster University, Hamilton, Ontario. Rapid cooling minimizes the chances of serious injury from heat stroke, which can include kidney damage and blood clots, says Dr. Sutton.

Running in the early morning or after sun-down on hot summer days will reduce the risk of heat stroke. Reducing speed and distance of running on hot, humid days will also help.

The casual weekend jogger out for a leisurely trek of two or three miles probably will not run a risk of heat stroke, unless he is in poor physical condition. Those beginning to run again this spring after a winter

of inactivity are advised to start with long walks and begin running slowly and gradually.

RISK OF SKIN CANCER FROM TANNING EVALUATED

CHICAGO — An older person who tans poorly is at increased risk of skin cancer from tanning.

Excessive exposure to sunlight increases the risk of skin cancer. But some individuals are much more likely to get skin cancers from excessive tanning than others.

Risk factors involved in skin cancer from sunning are tabulated in a report in an *American Medical Association* publication, *Archives of Dermatology*.

Dr. Peter Paul Vitaliano of University of Washington, Seattle, summarizes research findings:

1. With enough exposure, anyone is at substantial risk for skin cancers.
2. The effects of sun exposure take 20 or more years to become evident. The young sun enthusiast should be made aware of the consequences of repeated exposures, especially if he or she does not tan easily.
3. Given the same amount of exposure, older subjects are more susceptible to skin cancers than are younger subjects.
4. The ability to tan is a greater deterrent to skin cancer than is a dark complexion.

THALIDOMINE FOUND HELPFUL IN TREATING SKIN DISEASE

CHICAGO — Thalidomide, the well know drug

that caused many cases of birth defects in European babies in the 1960's is still being studied by researchers, and has been found useful in treating a particular skin infection, says a report in the current issue of an American Medical Association publication.

The drug has continued to be available under the trade name of Kevadon, for experimental purposes only. It is not licensed for other than research purposes.

Hans van den Broek, MD, of the Hines Veterans Administration Hospital, Hines, Ill., and the University of Illinois, Chicago, reports in *Archives of Dermatology* on successful treatment of a case of prurigo nodularis, a skin ailment that causes rash and growths like boils.

Most therapies for prurigo nodularis have been unsuccessful, and some sufferers have been plagued with the disease for years. Dr. Broek read a report from Jerusalem of successful treatment with thalidomine in three cases, and decided to try it on his Illinois patient. Over a period of three months the lesions gradually flattened and the itchy rash disappeared.

Aside from its well-known effect of causing birth defects, thalidomide has been shown to be virtually nontoxic. Suicide attempts with large amounts of the drug have been unsuccessful, and patients recovered after a period of sleep.

The patient had at time of writing been on the drug for eight months, and the dosage was slowly being lowered in an attempt to find the lowest effective maintenance dose. He has shown no ill effects from the drug.

Thalidomide still may be a useful drug for certain health problems, and is considered safe so long as it is not taken by expectant mothers.

DRUG FOR HIGH BLOOD PRESSURE EXONERATED AS CANCER CAUSE

CHICAGO — Reserpine, a drug product used by millions of Americans to control high blood pressure, is given a clean bill of health with regard to possible cause of breast cancer in a Mayo Clinic research report in the June 13 *Journal of the American Medical Association*.

Reserpine is prescribed for control of hypertension (high blood pressure) under several trade names — Lemiserp, Rau-Sed, Reserpoid, Sandril and Serpasil. Its value in controlling blood pressure has been well documented.

In the mid-70's reports first appeared of a possible link between reserpine and breast cancer in women. More than a dozen additional studies were conducted. The results disagreed, and both physician and patient have no clearcut guidelines.

Drs. Darwin R. Labarthe and W. Michael O'Fallon of the Mayo Clinic, Rochester, Minn., conducted a study of nearly 2,000 hypertensive women residing in Rochester to evaluate any possible relationship between hypertensive drugs and breast cancer.

Drs. Labarthe and O'Fallon found that women taking reserpine had no more breast cancer than women in the population at large.

They conclude:

"We have found no evidence of an association between exposure to either reserpine or thiazide diuretics (another useful drug) and the subsequent occurrence of breast cancer in hypertensive women."

LEGIONNAIRES' DISEASE MAY KILL 70,000 ANNUALLY

CHICAGO — Unrecognized cases of Legionnaires' Disease may be killing more than 70,000 Americans annually, says a research report in the June 13 *Journal of the American Medical Association*.

Columbus, Ohio, scientists examined lungs from 224 patients at autopsy and found a number of them had been infected with the organism of *Legionella pneumophila*, although deaths had been ascribed only to pneumonia.

Legionnaires' Disease may cause up to 3.6 per cent of the pneumonias in central Ohio, says Dr. Dale Fay. If this local incidence is extrapolated to the number of annual adult deaths in the United States, an estimate of 71,370 unrecognized adult Legion-

naires' Disease associated deaths annually may be made, Dr. Fay declares.

Many of the Legionnaires' Disease patients will have terminal illness of another type, so they would not benefit from appropriate therapy, the report points out. However, a substantial number may be basically healthy, and therapy may be life-saving.

Diagnosis of Legionnaires' Disease is most difficult for the physician, Dr. Fay emphasizes and "until prospective diagnostic techniques become available, recognition of the disease must depend on clinical acumen if mortality is to be kept within acceptable limits."

Some of those individuals whose lungs revealed the Legionnaires' Disease organisms had shown no important respiratory symptoms of fever, although pneumonia contributes considerably to their deaths, the study found. Only if the hospital conducts a routine laboratory examination of lung tissue at autopsy will a community know the true incidence of Legionnaires' Disease, the doctor says.

HARD WATER DISCREDITED AS HEART DISEASE PREVENTIVE

CHICAGO — The premise that hard water protects against heart disease, which has been studied for more than 20 years, is "untenable and probably incorrect," says a research report in the June 20 Journal of the American Medical Association.

Public health officials, particularly those charged with supervising public water supplies, have been aware of this premise for two decades. Many studies have been carried out, and recommendations have been made urging caution about softening drinking water. But the evidence has not been conclusive enough to bring a halt to softening water in the treatment process. Soft water is so much more useful in washing clothes and dishes and bathing that public health authorities have been reluctant to switch to hard water.

Drs. Douglas I. Hammer of Raleigh, N. C., and Siegfried Heyden of Duke University Medical Center, Durham, point out that their studies show

that "simple correlation studies, statistical studies and direct risk-factor studies all have failed to implicate water hardness and heart disease mortality in a consistent and causal fashion during the past 20 years."

"The time has arrived to turn our attention to more productive and more important research matters. It is certainly imperative to state that at present, setting standards for water hardness in the United States is not scientifically justifiable," Drs. Hammer and Heyden declare.

Changes in water hardness certainly cannot explain the striking decline in U. S. coronary and cardiovascular disease mortality, they point out. No major change took place in U. S. water hardness between 1968 and 1978, but deaths from those diseases dropped markedly. They credit reduced smoking, change in diet, control of high blood pressure, exercise programs and improved medical and hospital care for the reduction.

J. A. Bell of the AMA's Department of Environmental, Public and Occupational Health, points out that the process of softening water adds salt, and that it may be necessary for those persons on a strict low-salt diet to use bottled water in areas where the water supply is artificially softened.

CIGARETTE SMOKING BLAMED IN MINERS' LUNG DISEASE

CHICAGO — Cigarette smoking is the true culprit in causing lung disease in coal miners, says a report in the June 20 Journal of the American Medical Association.

And the incidence of truly disabling Black Lung Disease among miners has been greatly overstated, the report declares.

A report from the University of West Virginia Medical Center, Morgantown, points out that of 150 miners who claimed to be disabled from inhaling coal dust, only eight actually had significantly impaired breathing function, and none had the severe problem of progressive massive fibrosis (PMF), "the only true disabling form of coal workers' pneumoconiosis."

All of the 150 were cigaret smokers, says W. Keith C. Morgan, MD.

"There are several lessons to be learned from our experience of examining this series of Black Lung claimants. First and foremost, substantial and disabling ventilatory impairment is distinctly uncommon in claimants for Black Lung compensation. The only inferences that can be drawn from these data are that either disabling airway obstruction in the absence of PMF is no more common than in the general population, or that coal miners have a type of disabling respiratory impairment that is not detected by spirometry (the standard testing device for breath capacity)."

Some authorities have held that the latter conclusion may be true, and that an additional test of blood gases is necessary to test miners' breath volume properly. Dr. Morgan's report is a comparative study of miners tested with both spirometry and blood gases studies. He found no difference in the findings of the two methods and concludes that the blood gas studies are a waste of money.

"Surely the time has come to compensate those who are truly disabled, whatever the cause, be it occupational or otherwise, and furthermore, to award equal compensation for equal disability. But, let us not try to delude ourselves that coal mining leads to disability respiratory impairment in the absence of PMF."

In an accompanying editorial, JAMA Editor Willima R. Barclay, MD, himself a specialist in diseases of the chest, points to the Black Lung Benefits Reform Act of 1977 as a law "difficult to administer and often resulting in an unfair and inequitable distribution of public funds. Disability, even when it exists, is rarely caused by coal particles alone but is usually the result of other factors, such as cigarette smoking.

"A man in who emphysema develops and who has a history of being a coal miner can receive compensation, while another victim of the same disease, who never worked in a coal mine, receives no compensation."

Dr. Barclay charges that "the prospect of being awarded a government pension creates symp-

toms in many miners, who on careful examination have no organic basis for such symptoms. Unless a physician exercises great care in assessing those who wish to claim benefits, and unless sound and honest scientific judgment prevails over the wish to be a kindly benefactor, one more improper drain on the public treasury will take place."

Of all those eligible for benefits under the Black Lung Act, "only those who have smoked cigarettes, as well as mined coal, will qualify when subjected to rigorous pulmonary function testing."

ANNOUNCEMENT FROM THE UNITED STATES-CANADIAN DIVISION of the INTERNATIONAL ACADEMY OF PATHOLOGY, INC.

The Seventieth Annual Meeting of the United States - Canadian Division of the International Academy of Pathology will be held at the Palmer House in Chicago, Illinois, from Monday morning, March 2 through Friday evening, March 6, 1981. The Maude Abbott Lecture entitled "The Impact on Time on the Diagnosis and Treatment of Cancer: 1936-1981," will be delivered by Dr. Lauren V. Ackerman on Tuesday, March 3.

Scientific Papers, Poster Sessions, twelve Specialty Conferences, and 50 Short Courses are scheduled. A Special Course will be offered on "Immunopathologic Techniques in Diagnostic Pathology" with Dr. Robert T. McCluskey as Course Director. The Long Course will be on "The Inflammatory Process and Infectious Disease." with Drs. Guido Majno and Ramzi Cotran, Course Directors.

Further information about the meeting and courses may be obtained from Dr. Nathan Kaufman, Secretary-Treasurer, United States - Canadian Division of the International Academy of Pathology, 1003 Chafee Avenue, Augusta, Georgia, 30904. Telephone (404) 724-2973.

C U R S O S

THE AMERICAN COLLEGE OF CARDIOLOGY invites you to a program directed by: Douglas P. Zipes, MD, FACC - **PACING FRONTIERS: PHYSIOLOGICAL PACING AND ARRHYTHMIA CONTROL** - September 15 and 16, 1980, to be offered at the Heart House Learning Center, 9111 Old Georgetown Road, Bethesda, Maryland. For further information contact: Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland, 20014.

FROM THE AMERICAN COLLEGE OF PHYSICIANS

MKSAP COURSES - GROUP D - A series of four- and five-day courses covering Allergy and Immunology, Cardiovascular Diseases, Dermatology, Endocrinology and Metabolism, Gastroenterology, Hematology, Infectious Diseases, Nephrology, Neurology, Oncology, Pulmonary Diseases and Rheumatology.

COURSE NO. D08

Burlington, VT July 7-11
Co-Sponsor: University of Vermont College of Medicine
Director: Stanley Burns, Jr., MD, FACP

COURSE NO. D09

Detroit, MI July 21-25
Co-Sponsors: Henry Ford Hospital, Michigan State University College of Human Medicine; University of Michigan Medical School; and Wayne State University School of Medicine
Director: Boy Frame, MD, FACP

COURSE NO. D10

Atlanta, GA July 21-25
Co-Sponsors: Emory University School of Medicine; Medical College of Georgia School of Medicine, Medical University of South Carolina College of Medicine; and University of South Carolina School of Medicine
Director: J. Willis Hurst, MD, MACP
Co-Directors: David Propert, MD, ACP, Member Joseph Ross, MD, and Paul D. Webster, MD

COURSE NO. D11

Kansas City, KS July 28-31
Co-Sponsors: University of Kansas College of Health Sciences and Hospital and Wichita Campus, University of Kansas School of Medicine
Director: Norton J. Greenberger, MD, FACP
Co-Director: Martin Welch, MD, FACP.

COURSE NO. D12

Honolulu, HI July 28-Aug. 1
Co-Sponsor: University of Hawaii John A. Burns School of Medicine
Director: Irwin J. Schatz, MD, FACP
Co-Director: Dennis R. Meyer, MD, ACP, Member

COURSE NO. D13

Los Angeles, CA July 28-Aug. 1
Co-Sponsor: University of Southern California School of Medicine with faculty from: University of California, Irvine, California College of Medicine; UCLA School of Medicine; University of California, San Diego, School of Medicine; and Loma Linda University School of Medicine
Director: Phil R. Manning, MD, FACP
Co-Director: Varner J. Johns, Jr., MD, FACP

COURSE NO. D14

Louisville, KY July 29-Aug. 2

Co-Sponsor: University of Louisville School of Medicine

Director: Robert D. Lindeman, MD, FACP

Co-Director: Norman A. Cummings, MD

COURSE NO. D15

Pittsburgh, PA

Aug. 20-24

Co-Sponsors: Marshall University School of Medicine; University of Pittsburgh School of Medicine; and West Virginia University School of Medicine

Director: William M. Cooper, MD, FACP

Co-Directors: Maurice A. Mufson, MD, FACP and Robert H. Waldman, MD, FACP

COURSE NO. D16

Little Rock, AR

Aug. 25-28

Co-Sponsors: Louisiana State University School of Medicine in Shreveport; University of Arkansas College of Medicine; and University of Mississippi School of Medicine

Director: Peter O. Kohler, MD, FACP

Co-Directors: Marion D. Hargrove Jr., MD, FACP and Harper Hellums, MD

COURSE NO. D17

New York, NY

Aug. 25-28

Co-Sponsors: Albert Einstein College of Medicine

of Yeshiva University; Columbia University College of Physicians & Surgeons; Cornell University Medical College; New York Medical College; New York University School of Medicine, and The Page & William Black Post-Graduate School of Medicine.

Co-Directors: Samuel Elster, MD, FACP, Richard Gorlin, MD, FACP, and Fenton Schaffner, MD, FACP

COURSE NO. D18

Chicago, IL

Aug. 25-29

Co-Sponsor: Loyola University of Chicago Stritch School of Medicine; Northwestern University Medical School; Rush-Presbyterian-St. Luke's Medical Center; University of Chicago Pritzker School of Medicine; and University of Illinois College of Medicine

Director: Armand Littman, MD, FACP

COURSE NO. D19

Cleveland, OH

* Sept. 1-5

Co-Sponsors: Case Western Reserve University School of Medicine; Medical College of Ohio at Toledo; and Northeastern Ohio Universities College of Medicine.

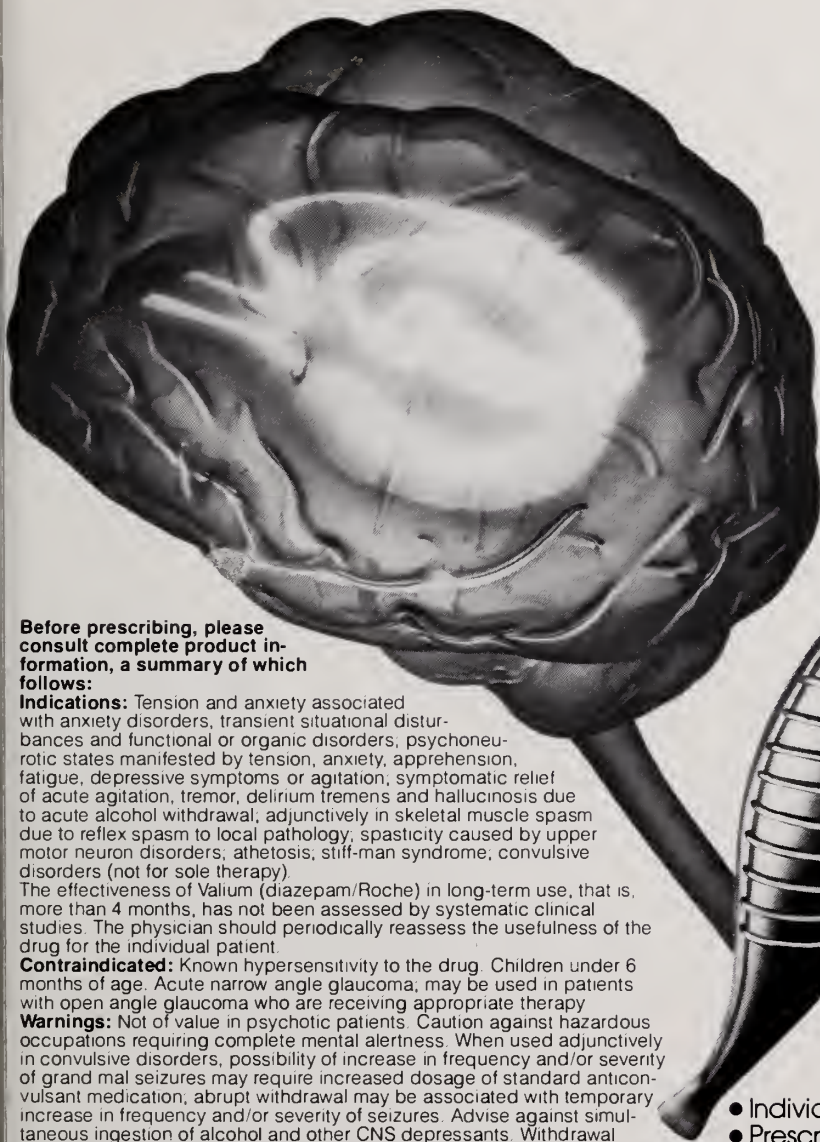
Director: Leigh Thompson, MD

ANUNCIO

Se vende o cambia por finca u opción a finca oficina amueblada, aire central, alfombrada. Opción \$24,000. Llamar 761-7894 después de 4:30 p.m.

ACADEMIC POSITION AVAILABLE — RADIO-THERAPIST - FULL TIME - ASSISTANT PROFESSOR IN RADIATION ONCOLOGY

Applicants must be certified by American Board of Therapeutic Radiology. To perform patient care, teaching and research duties at the Radiation Oncology Division, University of Puerto Rico School of Medicine. Both Spanish and English are required. Salary - \$26,000/year. Address: Radiation Oncology Division, Center for Energy and Environment Research, Caparra Heights Station, San Juan, Puerto Rico 00935.



Only Valium® (diazepam/Roche)
is indicated in anxiety
and tension states
and as an
adjunct in the
relief of skeletal
muscle spasm

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety associated with anxiety disorders, transient situational disturbances and functional or organic disorders, psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

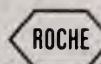
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. **Adults:** Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d., adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available in trays of 10.

General guidelines
for the prescribing
and appropriate use of
minor tranquilizers

- Individualize dosage for maximal beneficial effect.
- Prescribe the specific quantity needed until the next checkup period, schedule frequent, periodic reexaminations to monitor results of therapy.
- Establish treatment goals and gradually discontinue medication when these have been met.
- Avoid prescribing for individuals who appear dependency-prone or whose histories indicate the potential for misuse of psychoactive substances, including alcohol.
- Caution patients against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving.
- Advise patients against the ingestion of alcoholic beverages while undergoing therapy with minor tranquilizers.
- Counsel patients to follow label directions, keep medication out of children's reach, and dispose of unused or old medication.
- Caution patients against giving medication to others.
- Avoid abrupt cessation of extended therapy by tapering dosage before discontinuing medication.



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Nutley, New Jersey 07110

Only Valium® (diazepam/Roche)
has these two distinct effects

mind & muscle



-Antianxiety

-Skeletal
muscle
relaxant

2-mg, 5-mg, 10-mg
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Indicated in anxiety and tension
states and as an adjunct in the
relief of skeletal muscle spasm

Please see summary of
product information
on preceding page.

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BOLETIN

ASOCIACION MEDICA DE PUERTORICO

CONTENIDO:

VACUNACION: PRINCIPIOS Y PRACTICA 1980
REVISION Y CONCEPTOS - PARTE II
Rubella, Influenza, Vacuna Neumocócica, Paperas
Meningococos, Viajes al Extranjero

BRIEF COMMUNICATION: ARE WE ORDERING UNNECESSARY
AMYLASE STUDIES?

PROGRESO TERAPEUTICO: LAS TETRACICLINAS

INFECCION POR TUBERCULOSIS EN LOS ESTUDIANTES
DE MEDICINA DEL NIVEL PRECLINICO

EDITORIAL: ANGINA PECTORIS WITH NORMAL CORONARY ARTERIOGRAMS

GRAPHICS

MEDI-QUIZ

ABSTRACTOS DE LITERATURA MEDICA

CURSOS - NOTICIAS

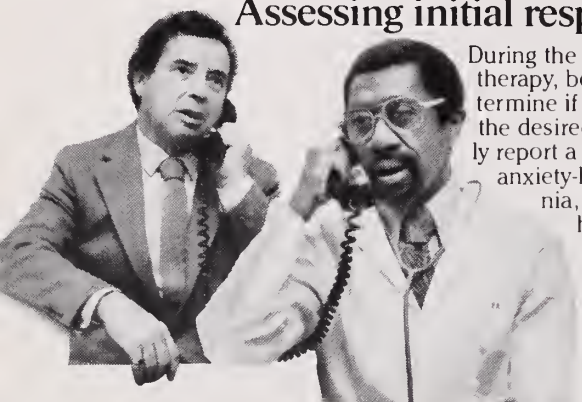
INDICE PAGINA 401

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OCT 31 1980

Monitoring patient response to Valium® (diazepam/Roche)

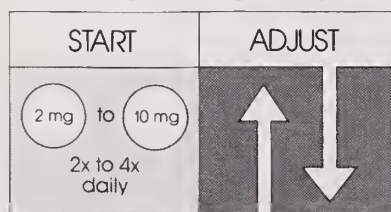
Assessing initial response to therapy



During the first follow-up visit after initiating therapy, both physician and patient should determine if Valium (diazepam/Roche) is having the desired effect. Most patients will promptly report a feeling of relaxation and relief of anxiety-linked symptoms such as insomnia, headaches, palpitations and hyperventilation. You will probably observe that the patient is calmer and more relaxed. If, however, patient response does not measure up to expectations, a reevaluation of the patient's profile with modification of the dosage regimen should be considered.



Making dosage adjustments



With any psychoactive medication it is good medical practice to initiate therapy at base dosage levels and titrate to the patient's needs. With Valium, experience has shown that 5 mg t.i.d. is usually sufficient although some patients with severe or persistent anxiety may require higher dosages initially. In geriatric or debilitated patients, the recommended dosage is 2 to 2½ mg once or twice daily.

When anxiety fluctuates, as is common with most patients, the dosage may be adjusted as needed during the course of therapy; three strengths in scored tablets give you unmatched flexibility and simplicity in individualizing dosage.

Evaluating progress toward therapeutic goals

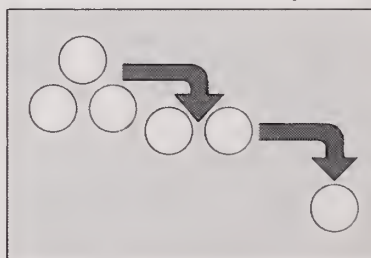
SET GOALS						
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

At the beginning of therapy it is now common practice for both physician and patient to establish treatment goals and to estimate the amount of time needed to achieve them. Then the patient knows what to expect and when to expect it.

Some physicians find that compiling a checklist of present-ing symptoms and complaints is useful for assessing the patient's response from visit to visit. In this way, progress toward attainment of the therapeutic goal is reviewed at regular intervals. As patients feel their symptoms abate and begin to develop insight into the sources of their anxiety and psychic tension, the checklist can be expected to dwindle.

Discontinuing pharmacologic intervention

When you decide to discontinue therapy, tapering dosage is good medical practice. Although rarely necessary after short-term treatment with Valium, gradual dosage reduction is advisable for patients who have been on extended therapy. This gradual discontinuance should preclude either recurrence of pretreatment symptoms or development of untoward side effects. Symptoms of withdrawal have almost always been associated with abrupt discontinuance of therapy at higher dosages taken continuously over long periods of time.



2-mg, 5-mg, 10-mg scored tablets
Valium®
diazepam/Roche

An Important Adjunct to Your Treatment Program for Excessive Anxiety

Valium® (diazepam/Roche) ®

Before prescribing, please consult complete product information, a summary of which follows:

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The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. **Adults:** Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed, adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500. Tel-E-Dose® packages of 100 available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10. Prescription Paks of 50, available in trays of 10.



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ASOCIACION MEDICA DE PUERTO RICO

SEPRE ESTE FECHA: NOV. 25 - 29, 1980

ASAMBLEA ANUAL

CENTRO DE CONVENCIONES

TYLENOL[®] with Codeine

tablets  / elixir 



mild to
moderate pain



moderate to
severe pain

Summary of Prescribing Information

Description

Tablets: Contain codeine phosphate* No. 1—7.5 mg. ($\frac{1}{8}$ gr.); No. 2—15 mg. ($\frac{1}{4}$ gr.); No. 3—30 mg. ($\frac{1}{2}$ gr.); No. 4—60 mg. (1 gr.)—plus acetaminophen 300 mg.

Elixir: Each 5 ml. contains 12 mg. codeine phosphate* plus 120 mg. acetaminophen (alcohol 7%)

*Warning: May be habit forming.

Actions: Acetaminophen is an analgesic and antipyretic; codeine an analgesic and antitussive.

Contraindications: Hypersensitivity to acetaminophen or codeine.

Warnings: *Drug dependence.* Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration; prescribe and administer with same caution appropriate to other oral narcotics. Subject to the Federal Controlled Substances Act.

Use in ambulatory patients. Caution patients that codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other CNS depressants. Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with this drug may exhibit additive CNS depression. When such a combination is contemplated, reduce the dose of one or both agents.

Use in pregnancy. Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.

Pediatric use. Safe dosage of this combination has not been established in children below the age of three.

Precautions: *Head injury and increased intracranial pressure.* Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions. Codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients. Administer with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: Most frequent: lightheadedness, dizziness, sedation, nausea and vomiting, more prominent in ambulatory than nonambulatory patients, some of these reactions may be alleviated if the patient lies down. Others: euphoria, dysphoria, constipation and pruritus.

Dosage and Administration: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. **TYLENOL with Codeine tablets** are given orally. The usual adult dose is: Tablets No. 1, No. 2, and No. 3. One or two tablets every four hours as required. Tablets No. 4. One tablet every four hours as required. **TYLENOL with Codeine elixir** is given orally. The usual doses are **Children (3 to 6 years):** 1 teaspoonful (5 ml.) 3 or 4 times daily. **(7 to 12 years):** 2 teaspoonfuls (10 ml.) 3 or 4 times daily. **(under 3 years):** safe dosage has not been established. **Adults:** 1 tablespoonful (15 ml.) every 4 hours as needed.

Drug interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings. For information on symptoms, treatment of overdosage, see full prescribing information.

Full directions for use should be read before administering or prescribing.

TYLENOL with Codeine tablets are manufactured by McNeil Laboratories Co., Dorado, Puerto Rico 00646.

Caution. Federal law prohibits dispensing without prescription.

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Fort Washington, PA 19034

In Fractures

Potent pain relief without aspirin complications



TYLENOL[®] with Codeine

tablets  / elixir 

Tablets Contain acetaminophen 300 mg plus codeine phosphate as follows:
No. 1—7.5 mg (1/8 gr); No. 2—15 mg (1/4 gr); No. 3—30 mg (1/2 gr); No. 4—60 mg (1 gr)
Elixir Each 5 ml contains 12 mg codeine phosphate* plus 120 mg acetaminophen (Alcohol 7%)

*Warning: May be habit forming

Please see facing page for summary of prescribing information

TIGHT CONTROL OF INFLAMMATION



in rheumatoid arthritis* and osteoarthritis:

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one capsule *t.i.d.*
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Double strength, nonsteroidal capsules offer...

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- **Dependable, long-term management of chronic symptoms**

Peak plasma levels are reached within 30 to 60 minutes. A therapeutic response can be expected in a few days to a week. And *Tolectin* tolmetin sodium is well tolerated: the frequency of milder gastrointestinal adverse effects and tinnitus has been shown to be less than with aspirin.

*For patients classified as Functional Class IV (incapacitated with little or no self-care), safety and effectiveness have not yet been established.

SUMMARY OF PRESCRIBING INFORMATION

TOLECTIN® DS (tolmetin sodium)

double-strength capsules—

for oral administration

Description: *TOLECTIN DS* (tolmetin sodium) capsules contain tolmetin sodium as the dihydrate in an amount equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium.

Contraindications: *Tolmetin* (tolmetin sodium) should not be used in patients who have previously exhibited intolerance to it or patients in whom aspirin and other non-steroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria.

Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported.

If *Tolmetin* must be given to patients with active peptic ulcer, closely supervise the patients for signs of ulcer perforation or severe gastrointestinal bleeding.

Precautions: *General*—Clinical studies of up to two years duration have shown no changes in the eyes attributable to *Tolmetin* (tolmetin sodium) administration; however, because of ocular changes observed clinically with other non-steroidal anti-inflammatory drugs, ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.

There has been no evidence of renal toxicity to date in clinical studies; however, since *Tolmetin* is eliminated primarily by the kidneys, closely monitor patients with impaired renal function; they may require lower doses.

Tolmetin prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when *Tolmetin* is administered.

In patients receiving concomitant *Tolmetin*-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

Tolmetin should be used with caution in patients with compromised cardiac function.

The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g. sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips (e.g. Albustix®, Uristix®, etc.).

Usage in Pregnancy—Since *Tolmetin* has not been studied in pregnant women, the use of *Tolmetin* during pregnancy is not recommended.

Nursing Mothers—Because *Tolmetin* may be secreted in human milk, as a general rule nursing should not be undertaken while a patient is on this drug.

Drug Interactions—Although *Tolmetin* has been found *in vitro* to bind extensively to plasma protein, it does not alter the dosage of warfarin required to maintain a uniform prothrombin time.

In adult diabetic patients under treatment with either sulfonylureas or insulin, there is no change in the clinical effects of either *Tolmetin* or the hypoglycemic agents.

Adverse Reactions: Gastrointestinal System—The most frequent adverse reactions which occurred were gastrointestinal: nausea, 1 in 9 patients; dyspepsia, 1 in 10 patients; abdominal pain, 1 in 15; gastrointestinal distress, 1 in 15; flatulence, 1 in 25; diarrhea, 1 in 25; constipation, 1 in 40; vomiting, 1 in 30; gastritis, 1 in 55; and significant gastrointestinal bleeding without evidence of peptic ulceration, 1 in 240.

The incidence of peptic ulcer in about 3000 patients treated up to two years in clinical studies was about 1 in 50. Thirty-four percent of the ulcer patients had prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs, including corticosteroids, known to produce peptic ulceration.

In clinical trials about 10% of patients dropped out because of adverse reactions, mostly gastrointestinal in nature.

Body as a Whole—headache, about 1 in 10 patients; asthenia and chest pain, less frequently; and, rarely, anaphylactoid reactions.

Cardiovascular—edema, about 1 in 15 patients; hypertension, less frequently.

Central Nervous System/Psychiatric—dizziness or lightheadedness, about 1 in 20 patients; tension or nervousness, 1 in 50 patients; drowsiness, 1 in 60 patients; insomnia and depression, less frequently.

Dermatologic—rash, about 1 in 40 patients; pruritus, 1 in 60 patients; skin irritation, 1 in 55 patients.

Special Senses—tinnitus, about 1 in 65 patients.

Hematologic—Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred. This is similar to that reported with other non-steroidal anti-inflammatory drugs. A few cases of granulocytopenia have been observed.

Caution: Federal law prohibits dispensing without a prescription.

Full directions for use should be read before administering or prescribing.

For information on symptoms and treatment of overdose, see full prescribing information.

Also available: *TOLECTIN®* (tolmetin sodium) tablets 200 mg. DEPT STOCKED 500's.

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ASOCIACION MEDICA DE PUERTO RICO

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ASOCIACION MEDICA DE PUERTORICO

VOLUMEN 72

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(haloperidol)
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Controls disturbed behavior in elderly patients without undue sedation*

Highly effective for psychotic symptoms...

such as irrational behavior, confused thinking, agitation, hyperactivity, emotional withdrawal, hostility, suspiciousness. "The ability of haloperidol [HALDOL[®]] to control troublesome symptomatology while preserving alertness and sociability would contribute significantly toward satisfying treatment goals and providing a better quality of daily life for the geriatric patient."

Smith GR et al. *Psychosomatics* 15:138, 3rd quarter, 1974

Minimizes likelihood of cardiovascular complications,** uncomfortable anticholinergic effects

"The lack of hypotensive effects ... suggests that haloperidol may be preferable to the phenothiazines in the treatment of mental disorders in the aged."

Tobin JM et al. *Geriatrics* 25(6):122, 1970

"Among the antipsychotic drugs...haloperidol has the lowest anticholinergic potential."

Bernstein JG. *Clinical Psychopharmacology*. Littleton, MA, PSG Publishing Company, 1978, p 123

Especially useful for treating elderly patients with concomitant diseases

Unlike some of the other major tranquilizers, HALDOL haloperidol may be used concomitantly with other medications frequently prescribed for geriatric patients.

"There really are no drug interactions of major clinical importance involving haloperidol, which is a rather unique advantage of this drug."

Bernstein JG. *Management of Side Effects Related to Antipsychotic Drug Therapy: An Interview*, 1978, p 12

* Although some instances of drowsiness have been reported, marked sedation is rare.

** Transient hypotension occurs rarely; severe orthostatic hypotension has not been reported.

Note: Extrapyramidal symptoms, when they occur, are readily controllable with antiparkinson drugs or dosage adjustment.

Please turn page for summary of prescribing information. Photograph posed by professional model.



concentrate
A tasteless, odorless, colorless Liquid Concentrate for better patient acceptability. 2 mg per ml haloperidol (as the lactate).

injection
A rapid-acting injection for psychiatric emergencies. 5 mg haloperidol (as the lactate) with 1.8 mg methylparaben and 0.2 mg propylparaben per ml, and lactic acid for pH adjustment to 3.4 ± 0.2 .

tablets
5 tablet strengths for convenience in individualizing dosage:
1 mg*, 2 mg, 5 mg*, 10 mg*, 1/2 mg

HALDOL[®] (haloperidol) *contain FD&C Yellow No. 5 (see Precautions)
tablets/concentrate/injection

A dosage form for every therapeutic need

Summary of Prescribing Information

Contraindications: Severe, toxic CNS depression or comatose states from any cause, hypersensitivity to the drug, Parkinson's disease

Warnings: Usage in Pregnancy: Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards. Infants should not be nursed during drug treatment

Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL haloperidol may block its vasopressor activity and paradoxical further lowering of blood pressure may occur); (2) receiving anticoagulant medication since HALDOL haloperidol may lower the convulsive threshold; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticonvulsants. Concomitant antiparkinson medication, if required, may have to be continued after HALDOL haloperidol is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL haloperidol. When HALDOL haloperidol is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL haloperidol. FD&C Yellow No. 5 (tartrazine) may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity

Adverse Reactions: CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug

may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn

Persistent Tardive Dyskinesia: Although rarely reported with HALDOL haloperidol, tardive dyskinesia may appear during or after long-term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and sometimes appear irreversible; there is no known effective treatment and all antipsychotic agents should be discontinued. The syndrome may be masked by reinstitution of drug, increasing dosage, or switching to a different antipsychotic agent.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms.

Cardiovascular Effects: Tachycardia and hypotension. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis, agranulocytosis rarely reported and only in association with other medication.

Liver Effects: Impaired liver function and/or jaundice reported. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair.

Endocrine Disorders: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia and hypoglycemia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Autonomic Reactions: Dry mouth, blurred vision, urinary retention and diaphoresis. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration.

The injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

Caution: Federal law prohibits dispensing without prescription.

IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

HALDOL tablets and concentrate (120 ml) are manufactured by McNeil Laboratories Co., Dorado, PR 00646.

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Fort Washington, PA 19034

VACUNACION: PRINCIPIOS Y PRACTICA 1980

REVISION Y CONCEPTOS – PARTE II

Rubella, Influenza, Vacuna Neumocócica Paperas, Meningococos, Viajes al Extranjero

Carlos H. Ramírez Ronda, MD, FACP, Paul Harrington, MD
Ramón H. Bermúdez, MD, FACP, José J. Gutiérrez, MD y
Guillermo Vázquez, MD

Resumen: El sarampión alemán o rubella es una enfermedad clínica benigna, cuyos efectos en el embrión son devastadores. Se discute la importancia de la vacuna en el control de las epidemias, al igual que los diferentes tipos de vacunas. Se presenta la estrategia de vacunación en Gran Bretaña y los E.U.A. El manejo de la mujer joven y el uso de vacunas en ésta se presenta. Los efectos secundarios se presentan en detalle.

La vacuna de la influenza se presenta en una perspectiva histórico epidemiológica. Se presenta su efectividad y los efectos secundarios y se discute el síndrome de Guillian-Barré asociado a la vacunación, especialmente la experiencia con la vacuna porcina.

La vacuna neumocócica es presentada, se discute su antigenicidad y su uso. Las indicaciones son presentadas y se enfatiza su uso cada 3 años.

Se presentan las indicaciones para la administración de la vacuna en contra de pa-

peras, el uso de la vacuna meningocócica en poblaciones militares y situaciones epidémicas. Los esfuerzos para producir vacunas en contra de *H. Influenzae* se menciona. La nueva vacuna en contra de la rabia originada en cultivo de tejidos humanos es presentada al igual que el uso de vacunas en contra de los herpes virus y gonorrea.

Se termina con las indicaciones para uso de vacunas cuando se viaja al extranjero.

Summary: German measles or rubella is a benign illness but whose effects on the embryo are devastating. The importance of rubella vaccine in the control of epidemics is presented as well as the different types of vaccines. The immunization strategies in Great Britain and U. S. A. is presented. The management of the young female exposed to rubella and the use of vaccines is presented.

Influenza vaccine is presented in a historical epidemiologic perspective. Its effectiveness and side effects as well as the Guillian-Barre Syndrome associated with the vaccine is discussed, specially the data with the porcine vaccine.

Pneumococcal vaccine, its composition, use, indications and antigenicity is discussed. Its use every 3 years is emphasized.

There are presentations on the indications for use of mumps vaccine, meningococcal

De los Departamentos de Investigación y Medicina, Hospital de Veteranos y Escuela de Medicina, Universidad de Puerto Rico, Laboratorio de Investigación en Enfermedades Infecciosas del Hospital de Veteranos y Programa de Entrenamiento en Enfermedades Infecciosas de la Escuela de Medicina, UPR y Hospitales Afiliados.

Favor pedir reimpresos a: Carlos H. Ramírez Ronda, MD, FACP, VA Med. & Reg. Office Center, Inf. Dis. Research Lab. (151), GPO Box 4867, San Juan, P. R. 00936.

vaccine. The efforts to have new vaccines for *H. Influenzae* is presented. The new rabies vaccine is presented as well as the status of herpes viruses and gonorrhea vaccines.

We finish with a review of the indications for vaccines when the patient is going on a trip to a foreign country.

Rubella

La rubella (35, 47) se consideró por mucho tiempo una enfermedad de la niñez. En el 1941, en un tratado clásico, Sir Norman Gregg, un oftalmólogo australiano, reconoció la asociación entre cataratas congénitas y la incidencia de rubella en la madre durante el primer trimestre del embarazo. En el 1962, dos grupos de investigadores aislaron independientemente el virus de rubella en cultivos de tejidos. Weller y Neva aislaron el virus de rubella en células humanas amnióticas primarias; Parker y Meyer aislaron el virus en cultivos de tejidos de riñón del mono verde africano utilizando el principio de interferencia. Por lo tanto, la infección de las células por el virus de rubella prevenían el efecto citopático producido por una super infección de las células por el virus Eco 11. Estos hallazgos a la luz de la epidemia nacional de rubella en 1964 llevaron al conocimiento de las tasas exactas de deformidad fetal que seguían a la rubella y al conocimiento de la clínica del síndrome de rubella congénito. Parkman y Meyer lograron atenuar el virus de rubella sin ocasionar la pérdida de su antigenicidad mediante pasajes seriados en cultivos. Esta cepa de virus, la HPUV-77, fue entonces pasada a través de embriones de patos y de células de riñón de perros dando como resultado dos vacunas que fueron utilizadas experimentalmente en humanos. Los investigadores en Europa atenuaron el virus de rubella pasándolo por células

de riñón de conejo y eventualmente produjeron la vacuna Candehill. Plotkin y asociados produjeron la vacuna atenuada del virus en células WI-38, la cual es conocida como la RA 27/3. El virus de la vacuna producido en células de riñón de perros fue más tarde removido cuando se encontró que este producto producía una alta tasa de artralgias y artritis como efectos secundarios. La vacuna RA 27/3 está en el mercado de los Estados Unidos, como se conoce en el substrato que se produce y por su pureza antigénica tiende a tener unos títulos de anticuerpos neutralizantes altos y sostenidos (47).

La estrategia de vacunación en los Estados Unidos difiere de aquella que se utiliza en Inglaterra (47). En los Estados Unidos las epidemias nacionales de rubella ocurren a intervalos de 6 a 9 años. Después de la epidemia de 1964 se percataron que podría ocurrir otra epidemia en gran escala durante los años 1970. Consecuentemente, la estrategia de inmunización de rubella en los Estados Unidos consiste en administrar la vacuna a niños entre las edades de 1 a 9 años con la provisión de que las mujeres que estén entrando en la edad en que puedan quedar embarazadas se les haga serología para constatar si tienen inmunidad en contra de rubella mediante la prueba de hemaglutinación e inhibición. Las mujeres con resultado negativo para la prueba deben inmunizarse siempre y cuando se provea para que estas no queden embarazadas por lo menos hasta dos meses después que se hayan vacunado. En Inglaterra se ha utilizado para la prevención de rubella, la detección de niñas adolescentes y mujeres que sean negativas para anticuerpos de rubella por la prueba de hemaglutinación e inhibición y su inmunización subsiguiente siempre y cuando estas no queden embarazadas en los próximos dos meses. En los Estados Unidos la incidencia de rubella

y la ocurrencia del síndrome de rubella congénita ha disminuído marcadamente. Existe actualmente un grupo grande de personas que van a llegar a la adolescencia y a la adultez joven que han escapado a la infección natural por caer fuera de los grupos que se estaban inmunizando. La inmunización en masa previno que el virus de rubella ocurriese en la población y estas personas por consiguiente escaparon a la infección natural. Como consecuencia de estos eventos y a la luz de los nuevos conocimientos de que la rubella puede diseminarse en poblaciones de individuos a pesar de que haya presencia de inmunidad del grupo, las epidemias de rubella ocurren ahora regularmente en escuelas superiores, colegios y poblaciones de reclutas. Se estima que hasta que no se lleve a cabo la inmunización mandatoria por lo menos el 15 por ciento de las mujeres jóvenes continuarán sin inmunidad a rubella. Para mantenernos relativamente libres del síndrome de rubella congénita, es esencial la inmunización de las mujeres que tengan negativa la prueba serológica. La prueba Rubacel de los Laboratorios Abbott emplea el principio de hemaglutinación pasiva, es menos costosa que la prueba de inhibición de hemaglutinación e inhibición que se emplea rutinariamente y puede utilizarse extensamente para detectar estas mujeres no inmunes. Las mejores ocasiones para constatar la inmunidad de rubella en mujeres jóvenes son: 1) durante el examen premarital serológico; 2) la visita inicial de la mujer joven al gineco-obstetra y en tercer lugar el período post parto. Este período es también útil para llevar a cabo la inmunización siempre y cuando se provean los medios para evitar embarazos durante los dos meses subsiguientes (48).

La inmunidad a rubella se refleja en los anticuerpos séricos neutralizantes los cuales correlacionan muy bien con la prueba de he-

maglutinación e inhibición. Después de la inmunización en contra de rubella, aproximadamente el 95 por ciento de las personas desarrollaron anticuerpos. El nivel sérico de anticuerpos es menor que el nivel después de una infección natural por rubella. Las pruebas de fijación de complemento rara vez se tornan positivas después de la inmunización por rubella, no obstante, algunos de estos títulos pueden estar aumentados transitoriamente después de una infección natural por rubella. La vacuna de rubella fue autorizada en 1969 y todavía es muy temprano para determinar con certeza cuanto dura o durará la inmunidad después que se administre la vacuna. En los niños que no han estado expuestos a la reinfección se desarrollaron títulos de anticuerpos relativamente altos. Estudios seriados no han demostrado una tendencia para que el nivel de anticuerpos disminuya significativamente. Aquellos que tienen un nivel de anticuerpos iniciales más bajo tienen la tendencia de que sus niveles de anticuerpos se conviertan en no detectables con el transcurso del tiempo, a pesar de que estos niños tienen una respuesta anamnésica cuando son reinmunizados (49, 50, 51). Se sabe que en personas que tienen inmunidad natural a rubella puede ocurrir la reinfección (47). En pacientes que han recibido la vacuna de rubella también se ha demostrado la infección, pero sabemos que la viremia no ocurre en estas personas y que excretan el virus via la nasofaringe en títulos bajos, por lo tanto, no ponen en peligro a las personas que están en contacto con ellos. Los individuos que reciben la vacuna rara vez transmiten el virus a los contactos cercanos.

Los efectos secundarios son pocos en número (47). Aproximadamente el cinco por ciento, particularmente las mujeres jóvenes desarrollaron artralgias o artritis transitorias (52, 53). Estas usualmente desaparecen

de uno a tres días a pesar de que en algunas ocasiones las artralgias pueden persistir por un período más largo. Las personas que reciben la vacuna pueden desarrollar signos y síntomas relacionados a neuropatía periférica con parestesias (54). Los niños pueden asumir una posición característica, conocida como la posición del receptor o en cuclillas. Estos síntomas que hemos mencionado pueden desarrollarse tardíamente. El mayor problema con la vacuna reside en su potencial para cruzar la placenta y tener efectos teratogénicos (47). Por lo tanto, una mujer embarazada no debe ser vacunada o debe de evitar el embarazo durante los dos meses posteriores a la inmunización. En autopsias de fetos abortados se ha demostrado que el virus de la vacuna puede ser recobrado del tejido fetal inclusive de estructuras tales como el ojo. Un número limitado de mujeres que ha recibido inadvertidamente la vacuna durante el embarazo y que eran no inmunes en el momento de su vacunación han sido llevadas a término con partos de niños normales. El número es pequeño y no excluye el hecho de que el virus de la vacuna puede ser un teratógeno menor. Conociendo la evidencia de que hay un número de anormalidades congénitas que se presenta con cualquier embarazo, es posible que algunas de estas anormalidades congénitas puedan ser adscritas a la vacuna. Por consiguiente, si una mujer está embarazada en el momento en que se administra la vacuna y si puede demostrarse que en ese momento ella tiene una prueba de hemaglutinación/inhibición negativa, los criterios médicos aceptados dictan que deben de recomendarse a este paciente que se someta a un aborto terapéutico (47). Si el embarazo se desea o si la paciente es de edad mayor los riesgos deben de ser explicados al paciente. Bajo estas circunstancias y con un consentimiento informado completo, el embarazo puede llevarse

a término teniendo en mente la posibilidad de que mal formaciones relacionadas al virus de la vacuna no podían excluirse.

Influenza (55, 56)

La pandemia de influenza de 1918 al 1919, una de severidad inusitada, fue denominada como la gran plaga al causar aproximadamente 20 millones de muertes. En 1933 Laidlaw, Andrews y Smith aislaron el agente de la influenza. La vacuna de virus inactivada de influenza fue desarrollada y administrada a personal en el servicio militar durante la segunda guerra mundial. Durante las fases iniciales de vacunación los resultados fueron mayormente impredecibles porque había una falta de apreciación de lo que se conoce como el cambio antigénico y la variación antigénica de este virus. La vacuna también contenía muchas más impurezas que las que se preparan hoy, las cuales se purifican mediante técnica de ultracentrifugación de zona. En los primeros estudios quedó demostrado que la vacuna era efectiva en alrededor del 75 por ciento de las personas que la recibían. La vacuna protegía de la enfermedad si la estructura antigénica de ésta era similar a la del virus que está predominando durante la temporada en donde ésta se administraba. Al reconocer el fenómeno del cambio y la variación antigénica, la estrategia de vacunación se desarrolló de tal manera que cada uno de los antígenos mayores fue incluido en la vacuna, creando una vacuna polivalente. En la actualidad, los siguientes tipos antigénicos mayores del virus se reconocen que han circulado en la población: $H_{sw}N_1$, H_0N_1 , H_1N_1 , H_2N_2 . En los años 1940 y en los 50 se reconocían un número menor de antígenos, pero se aplicó el mismo raciocinio. Estas vacunas polivalentes inicialmente no fueron efectivas por

dos razones: 1) la variación de los diferentes determinantes antigénicos relativos al virus prototipo con el cual se manufacturaba la vacuna podían ser relativamente grandes. Por ejemplo, el prototipo del virus H_3N_2 es significativamente diferente del A-Hong Kong. 2) los efectos secundarios locales y sistémicos limitó la cantidad total del antígeno que podía incluirse en la vacuna. La respuesta serológica y por consiguiente el efecto protector está directamente relacionado a la masa antigénica que se incluía en la vacuna. El concepto de la vacuna polivalente se ha revitalizado si se logra obtener un adjuvante seguro, sin efectos secundarios, especialmente cuando la circulación no esperada del virus porcino y el virus A ruso.

Después que se demostró la ineffectividad del uso rutinario de la vacuna polivalente, se prepararon vacunas univalentes, bivalentes y como mucho trivalentes. La constitución antigénica de las vacunas es de suma importancia, ya que la constitución correcta dependerá de la capacidad de predecir que cepa en específico de un virus será la que circule. Esto a su vez dependerá del rastreo efectivo y la identificación del tipo de influenza que esté ocurriendo. En términos generales se ha pensado que una cepa de influenza A circulará en una población que tenga el nivel de inmunidad colectivo más bajo para esa cepa en específico. Una vez cada 10 años ocurre un cambio de antígenos mayores en el virus de influenza. Si este nuevo virus es capaz de circular en la población, entonces ocurrirán epidemias y pandemias. Estas generalizaciones fueron insuficientes para predecir con certeza y los años 1960 y 1970. Fue esta generalización en la cual se basó la campaña de influenza porcina. El fracaso de que el virus $H_{SW}N1$ no circulase en la población en general y el surgimiento inesperado de la nueva cepa A-USSR son ejemplos

de las dificultades inherentes en predecir correctamente la nueva cepa de influenza que causará enfermedad en la población. Antes de la campaña de inmunización para la influenza porcina (57, 58) se pensaba que la vacuna de influenza era inocua, especialmente desde el punto de vista en cuanto a posibles reacciones severas o secuelas a largo plazo (59, 62). Previo a que cesase la campaña para inmunizar la mayor parte de la población adulta de los Estados Unidos se administraron 42, 783 y 707 unidades de la vacuna. La campaña fue detenida cerca del 17 de diciembre de 1976. Hasta el 4 de febrero de 1977 se reportaron un total de 342 casos del síndrome de Guillain Barré en personas que habían sido vacunadas con la vacuna que contenía A-New Jersey. Durante el mismo período de tiempo ocurrieron 314 casos del síndrome de Guillain-Barré en personas no vacunadas. Ocurrieron 29 casos en personas que recibieron una vacuna de influenza diferente, la vacuna con el virus de Hong Kong y en donde el status de vacunación se desconocía. Los síntomas iniciales del síndrome de Guillain-Barré ocurrieron en su mayoría de dos a tres semanas después de la inmunización. El grupo de edad con mayor riesgo relativo fue el de las personas entre las edades de 25 a 44 años, el grupo que tenía el menor riesgo fueron las personas de 18 a 24 años de edad. La razón casos/fatalidad en pacientes vacunados y no vacunados desarrollando el síndrome fue similar, aproximadamente 4 por ciento. El número de casos con el síndrome de Guillain-Barré varió en las diferentes regiones del país, como por ejemplo: Pennsylvania reportando 18 casos en personas vacunadas y 6 casos en personas no vacunadas. Se calcula en base a los datos conocidos que podríamos esperar un caso del síndrome de Guillain-Barré de cada 80,000 personas que reciben la vacuna de influenza. Antes de la campaña de inmu-

nización para influenza porcina no existía la asociación de este síndrome con la vacuna de influenza. Miller y Stranton en su repaso de los síndromes neurológicos después de inmunización no mencionan la ocurrencia de estos síndromes después de la vacunación con influenza (4). Sin embargo, el artículo afirma que puede manifestarse después de una inoculación con cualquier producto biológico. No obstante, a pesar de que el síndrome de Guillain-Barré puede ser una seria complicación, la vacuna representa el arma más eficaz hasta el presente para prevenir la influenza en individuos predispuestos, ya que la enfermedad tiene una morbilidad y mortalidad significativa. Estas personas incluyen aquellas de 65 años de edad o más, y aquellas con enfermedades crónicas, particularmente las que tienen enfermedad cardíaca, enfermedad pulmonar o problemas metabólicos como diabetes mellitus (63-68). La vacuna inactivada de influenza representa la mejor medida de prevención cuando se utiliza durante las pandemias, particularmente cuando éstas son causadas por cepas virulentas del virus, como por ejemplo, la cepa de 1918-19. La administración de amantadina en una dosis para adultos de 100 mg dos veces al día puede y debe considerarse como un régimen profiláctico comparable en eficacia a la vacuna (69).

Una vacuna trivalente A-Texas, A-USSR, B-Hong Kong se encuentra en el mercado. La inmunización debe de ser dirigida como en el pasado a la prevención de morbilidad y mortalidad significativa en personas con predisposición a desarrollar enfermedad severa (67). No hay una campaña nacional encaminada a prevenir la enfermedad en personas más jóvenes. La enfermedad en la Unión Soviética se suscitó en su mayoría en personas jóvenes describiéndose como una enfermedad relativamente benigna con una

tasa baja de fatalidad. La vacuna es de virus completos o partidos (subunidades) (70, 71). En personas menores de 24 años, dos dosis de la vacuna son necesarias para lograr una respuesta serológica apropiada. En adultos una dosis es suficiente. Las vacunas de virus vivos que se han utilizado en pruebas clínicas han protegido en contra de inoculaciones artificiales y naturales. Estas vacunas se utilizan extensamente en el extranjero, pero en los Estados Unidos en el momento deben de considerarse como experimentales.

Vacuna Neumocócica (72)

El neumococo sigue siendo la causa predominante de pulmonía bacteriana. Se ha demostrado que la mortalidad temprana en personas hospitalizadas con pulmonía neumocócica no ha sido influenciada significativamente con el tratamiento antimicrobiano, cuando se comparan los datos con los de personas no tratadas o tratadas con tratamiento de suero específico en la era previa a los antibióticos (73). La otitis media en los niños es una causa significativa de morbilidad. La meningitis por neumococos tiene una tasa de mortalidad de aproximadamente 15 por ciento y en algunas otras series ésta es aún mayor. Además se reconoce que tanto niños como adultos a los que se le ha removido el bazo o que tienen disfunción de bazo funcional, tienen un alto riesgo de desarrollar bacteremia fatal (74). Los pacientes con anemia trepanocítica sufren de una tendencia aumentada a desarrollar pulmonías y meningitis por neumococos con una mortalidad alta (74). Recientemente, en dos localidades de Africa del Sur se ha encontrado una cepa de neumococos resistente a múltiples antibióticos incluyendo penicilina. Esta cepa era susceptible a los siguientes antibióticos: Bacitra-

cina, Novobiocina, y Vancomicina. Se ha detectado un aumento en la tasa de resistencia relativa del neumococo a penicilina en otros lugares como Nueva Guinea, Minneapolis, Minnesota, Oklahoma y Dallas. El mecanismo de resistencia del pneumococo a los antibióticos no es mediado por plásmidos y se cree ocurre debido a la capacidad disminuida del antibiótico a atravesar la pared bacteriana. Es probable que presiones selectivas de uso de antibióticos haya sido uno de los factores contribuyentes a aumentar la resistencia (75).

En los años treinta, el tratamiento con suero inmuno específico demostró tener un efecto terapéutico en la pulmonía neumocócica (76). Durante la segunda guerra mundial, la inmunización con la vacuna neumocócica cuatrivalente ofrecía protección significativa a aquellos inmunizados en contra de pulmonía inducida por los tipos neumocócicos presentes en la vacuna pero no en contra de los tipos heterólogos. La colonización neumocócica nasofaríngea fue significativamente reducida en el grupo estudiado, produciendo un efecto en disminuir las tasas de pulmonía (76).

Comenzando en el 1967 y culminando con la licencia de la vacuna neumocócica polivalente en 1978, Pneumovax[®], Austrian y sus colaboradores han estado trabajando en el desarrollo de una vacuna que prevenga la enfermedad neumocócica y disminuya el número de personas particularmente predisuestas a infecciones neumocócicas (73-78). Durante las etapas iniciales del estudio ellos determinaron que 14 serotipos de neumococos eran los causantes del 85 por ciento de los episodios de bacteremia neumocócica que ocurrían en los Estados Unidos. Varias vacunas experimentales fueron preparadas, cada una conteniendo 50 microgramos de antígeno polisacárido de cada uno de los serotipos que

se incluirían en la vacuna. Las vacunas diferían en el número de serotipos que se incluían. Después de una inyección se midieron los anticuerpos mediante radioinmunoensayo para cada uno de los serotipos antigénicos incluidos en la vacuna (76). Se encontró que la respuesta inmunológica era de larga duración y se extendió en la mayoría de los que recibieron la vacuna por lo menos hasta 24 meses. Las reacciones locales y sistémicas se suscitaron en alrededor de 40 por ciento de los recipientes y fueron de carácter menor y autolimitante. Los efectos secundarios se han detectado con más frecuencia en personas que reciben dosis múltiples de la vacuna y por esta razón tanto como por la evidencia de inmunidad continuada de la vacuna se recomienda el uso de Pneumovax no más frecuente de una vez cada 3 años (75).

La vacuna ha sido estudiada en varias pruebas de campo. Se comprobó que la vacuna significativamente reducía la pulmonía neumocócica y las bacteremias en un grupo de mineros de oro en Africa del Sur (76). Estudios controlados en Africa del Sur involucrando 12,000 mineros de oro han demostrado que la vacuna polivalente es 78.5 por ciento efectiva en prevenir casos confirmados radiológicamente de pulmonía y 82.3 por ciento efectiva en prevenir bacteremia neumocócica causada por los serotipos incluidos en la vacuna. Usando una vacuna octavalente, investigadores en San Francisco han demostrado una disminución significativa en la incidencia de enfermedad neumocócica en pacientes con anemia trepanocítica (74). Hasta el presente no existen estudios controlados que demuestran los efectos de la vacuna en la incidencia de enfermedad neumocócica en otros pacientes sin bazo (74). No existen estudios en el momento demostrando el efecto de la vacuna en pacientes con mieloma múltiple o leucemia crónica

linfocítica, dos condiciones las cuales están asociadas con un riesgo aumentado de enfermedad neumocócica. En el momento hay una serie de estudios en progreso que nos resolverán en forma definitiva estas preguntas sobre el uso de Pneumovax® en estos pacientes. Nosotros recomendamos el uso de esta vacuna en este grupo de pacientes hasta que se demuestre que no es efectiva. En el estudio original de MacLeod (76) durante la segunda guerra mundial y estudios subsiguientes demostraron una disminución en los portadores de neumococos en la nasofaringe. Este hecho potencialmente puede utilizarse para producir un efecto de inmunidad grupal para disminuir la incidencia de enfermedad neumocócica en los no inmunizados. La vacuna se recomienda para personas particularmente predispuestas a morbilidad y mortalidad significativa de infecciones neumocócicas. Esto debe incluir aquellas personas que tienen disfunción del bazo funcional, pacientes cuyo bazo fue removido por un proceso quirúrgico, personas con enfermedad pulmonar crónica, con enfermedad cardiovascular y pacientes con desórdenes metabólicos como diabetes mellitus. Además debe utilizarse de una manera experimental en pacientes con mieloma múltiple y leucemia linfocítica crónica y muy posiblemente en pacientes con enfermedad renal crónica.

Se necesita más experiencia clínica con la vacuna antes que estemos conscientes del espectro de los efectos secundarios. Con las preparaciones más antiguas de la vacuna neumocócica se informó de un caso de Guillain-Barré en un paciente que recibió la vacuna. Se ha suscitado la polémica de administrar o no penicilina profiláctica consecuentemente con la vacuna en pacientes sin historial de alergia. No se ha encontrado evidencia que demuestra que la profilaxis con penicilina sea efectiva. Sí sabemos que el uso

continuo de penicilina puede conllevar a un aumento en la resistencia del neumococo a antibióticos como penicilina en personas que están predispuestas a esta infección. En estudios previos con las vacunas neumocócicas más antiguas en Africa del Sur se comprobó que los serotipos de neumococos que no se incluían en la vacuna eventualmente reemplazaban los que estaban incluidos. Debe de mantenerse un rastreo de los serotipos serológicos del neumococo causando pulmonía y bacteremia en todo momento, de tal manera que la vacuna pueda modificarse para prevenir el fenómeno de infecciones con cepas resistentes o cepas no incluidas en la vacuna.

Otras Vacunas

Paperas

La vacuna en contra de paperas, la cepa Jerryl Lyn recibió su licencia en 1967. Es una cepa de virus atenuado vivo la cual induce inmunidad a largo plazo, según se comprobó por la protección en contra de la enfermedad y por la persistencia de títulos de anticuerpos de hemaglutinación e inhibición (79, 80). Sus efectos secundarios son extremadamente raros. Se puede utilizar con vacunas combinadas, por ejemplo, con rubella o con rubella y sarampión. En la combinación de vacunas con virus vivos se ha comprobado que estas pueden ser tan efectivas desde el punto de vista de seroconversión como cuando el individuo recibe solo una de ellas. Ya que las paperas es la causa principal de infertilidad secundaria en el hombre, se recomienda la administración de la vacuna para hombres jóvenes que han llegado a la adultez sin tener historial clínico de la enfermedad y que no han estado previamente inmunizados. La prueba de piel no constituye un índice de inmunidad. Las prue-

bas serológicas son necesarias para determinar inmunidad por lo tanto, las pruebas de neutralización o de hemaglutinación e inhibición son difíciles para hacerse rutinariamente en un laboratorio y se depende de laboratorios de referencias.

Meningococos

Gottlich, Goldschneider y Artenstein (81), como resultado del surgimiento de cepas de meningococos resistentes a sulfa durante los años 1960, desarrollaron vacunas en contra de los meningococos del grupo A y C que protegen en contra de infección por meningococos homólogos. Estas vacunas han eliminado casi totalmente el problema de infecciones meningocócicas por grupos A y C en los reclutas. Se ha demostrado que la vacuna grupo A es protectora en infantes hasta de tres meses (82). La vacuna del grupo C no es confiable para establecer la inmunidad en niños menores de dos años. En la práctica civil estas vacunas tienen un uso más apropiado en situaciones epidemiológicas específicas, cuando hay la posibilidad de que la enfermedad meningocócica sea por estos dos tipos y cuando se corra el riesgo de una epidemia en la población (83-90).

Hemophilus influenzae

Se ha tratado de producir una vacuna en contra del *Hemophilus influenzae* grupo B, la causa más común de meningitis en niños pequeños; los esfuerzos no han sido muy exitosos debido al hecho de que en niños menores de dos años de edad y candidatos a recibir la vacuna no se ha podido producir el estado de inmunidad consecuentemente.

Rabia

Es muy probable que una nueva va-

cuna antirrábica reemplaze la vacuna en embrión de pato que se ha venido utilizando desde el 1957 (91-93). La nueva vacuna antirrábica se produce en cultivos de tejidos humanos, la célula WI-38. La vacuna contiene una masa antigénica mayor y puede inducir la misma respuesta serológica que la vacuna de pato con una dosis menor. Los efectos secundarios aparentemente son de menor severidad.

Herpes Viruses

Otras vacunas virales que están en desarrollo incluyen aquella en contra del virus de herpes simplex tipo I y tipo II (92), y varicella zoster (93, 94, 95). Las vacunas en contra del virus de herpes simplex producidas en Europa y con nombres como Lupidon H (HSV-1) y Lupidon G (HSV-2) son vacunas de virus muertos de composición pobremente definida que no han sido demostradas científicamente que previenen infecciones herpéticas recurrentes. Estas vacunas han sido utilizadas mayormente en pacientes que han viajado a Europa a recibirlas. Debe notarse que un producto elaborado en los Estados Unidos de Norte América dirigido en contra de virus de herpes simplex tipo I fue usado por un tiempo y después de abandonado por ser inefectivo.

Cepas atenuadas de citomegalovirus están en proceso de desarrollo en los Estados Unidos e Inglaterra con el propósito de desarrollar una vacuna. Los recipientes potenciales de esta vacuna serían mujeres jóvenes, seronegativas que pueden quedar embarazadas y los recipientes de transplantes.

Una vacuna de virus vivo atenuado de varicella zoster está siendo desarrollada por un grupo de investigadores japoneses los cuales opinan que a pesar de que la mayor parte de los niños se infectan por este tipo

de virus puede que sea menos peligroso el inducir inmunidad, mediante una dosis controlada de la vacuna de virus atenuada (94). Este raciocinio se utilizará particularmente en niños que van a recibir o han recibido ya tratamiento inmunosupresivo para inducir la remisión de algún proceso maligno. El desarrollo de estas vacunas de varicella zoster ha sido detenido por el informe de un caso que evidenció la enfermedad diseminada en un niño inmunosuprimido el cual recibió la vacuna. Las vacunas atenuadas de virus pueden ser extremadamente difíciles, ya que todos los virus herpes que se incluyen en las vacunas pueden convertirse en latentes y pueden reactivarse más tarde.

Gonorrea

Una vacuna experimental en contra de la *Neisseria gonorrhoeae* (96) está en vías de desarrollo. ' Se ha tratado de producir una vacuna pero esto ha sido limitado por el número de tipos antigénicos del gonococo. Se están purificando antígenos los cuales aparentemente ofrecen protección en animales en contra de la mayor parte de las cepas de gonococos. Estos antígenos incluyen los componentes principales de la proteína de la membrana exterior, los antígenos capsulares y los antígenos en los pilis. La población hacia la cual se dirigirá esta vacuna serían aquellas personas que hayan sufrido previamente alguna enfermedad venérea, ya que éstos estarían a un riesgo más alto para desarrollar infección por gonococo.

La Vacunación en la Práctica de la Medicina

El médico necesita conocer los procesos de mantener al día el estado de la inmunización de sus pacientes, principalmente

en la práctica privada. La inmunización en la oficina privada puede ser llevada a cabo por el personal de la oficina siempre bajo la supervisión del médico. En otro tiempo en donde es conveniente asegurar el estado de inmunización del paciente es al finalizar cualquier hospitalización donde se ha obtenido un historial de inmunización completo y en detalle. El médico debe estar consciente de que los requisitos de inmunización cambian con el tiempo y que las indicaciones difieren entre los adolescentes, adultos jóvenes, el paciente envejeciente o el paciente con una enfermedad crónica. En la Tabla III presentamos las inmunizaciones que deben de estar al día tanto en pacientes adolescentes, adultos jóvenes y envejecientes la cual puede utilizarse como guía (97).

El Viaje al Extranjero

Bajo las reglas de salubridad internacional adoptadas por la Organización Mundial de la Salud algunos países requieren certificados de vacunación internacional en contra de cólera, viruela y fiebre amarilla para viajeros internacionales. La certificación para la inmunización de cólera es válida durante seis meses comenzando seis días después de la inoculación de la vacuna o comenzando a partir del día de re-vacunación si ésta ocurrió dentro de los primeros seis meses de la primera inoculación. El certificado para la inmunización de viruela es válido durante tres años comenzando ocho días después de la vacunación primaria o en el día de revacunación. El certificado para fiebre amarilla es válido durante diez años comenzando diez días después de la vacunación primaria o en el día de revacunación dentro de un período de diez años de la primera inyección. Algunos países no requieren ninguna de ellas o las requieren

TABLA III

Vacunación para Adultos

<i>Vacuna</i>	<i>Adolescente o Adulto Joven</i>	<i>Envejeciente, Adulto Madura o Paciente con Enfermedades Crónicas</i>
<i>Td</i>	<i>Serie primaria de 3 inyecciones, Td cada 10 años</i>	<i>Serie primaria de 3 inyecciones, Td cada 10 años</i>
<i>Influenza</i>	-----	<i>Anualmente</i>
<i>Pneumovax</i>	-----	<i>Cada 3 años</i>
<i>Poliomielitis</i>	<i>Coteje el estado de inmunización; administre la vacuna oral (OPV) trivalente solo si el paciente está o entrará en alto riesgo o, considere uso de vacuna Salk antes de la vacuna oral</i>	----
<i>Sarampión</i>	<i>Si no tiene historial de enfermedad y no se ha vacunado puede vacunarlo opcionalmente</i>	----
<i>Rubella</i>	<i>Vacune a las mujeres que tengan la prueba de HAI negativa, debe evi- tarse el embarazo por 2 meses</i>	----
<i>Paperas</i>	<i>Vacune a los varones sin historial de enfermedad de vacunación</i>	----

solamente si el viajero ha visitado recientemente un área endémica. Las otras vacunas que el viajero puede desear tener son solamente para su protección individual. Los beneficios que se pudiesen derivar de otros tipos de vacunación deben ser pesados en contra de los

efectos secundarios de las vacunas. También debe tenerse en consideración cuáles son los problemas potenciales para un norteamericano o un puertorriqueño visitando un país extranjero. Los problemas de salubridad para un ciudadano norteamericano visitando los países

en desarrollo incluyen malaria, hepatitis y diarrea. Excepto cuando la fiebre tifoidea fue epidémica en Méjico los problemas del viajero usualmente no incluyen cólera o fiebre tifoidea.

Hay tres factores que deben considerarse al decidir si un viajero necesitará inmunización en contra de viruela, cólera o fiebre tifoidea: (1) los requisitos para reingreso en los Estados Unidos de Norteamérica. Nuestro país requiere solamente un certificado de vacunación válido para viruela si el viajero ha estado en un área infectada dentro de 14 días, que es el período de incubación para viruela; (2) un conocimiento de cuál área del globo está infestada; para decidir ésto uno puede utilizar la organización mundial "Blue Shield" o "International Notes Quarantine Measures" publicado por el Centro para el Control de Enfermedades en su reporte semanal de morbilidad y mortalidad. El Departamento de Salud Pública o cualquier biblioteca médica usualmente tienen esta información. Algunos países requieren vacunación solamente si el viajero llega de un área infestada; (3) los requisitos de entrada para cada uno de los países en el itinerario; estos requisitos pueden ser mandatorios u opcionales dependiendo del área visitada por el viajero.

Se necesita conocer las áreas del globo infestadas para determinar requisitos de inmunización en contra de viruelas, fiebre amarilla y cólera. El último caso reportado de viruela ocurrió en Somalia. La transmisión de viruela se cree que ha finalizado. Si el viajero está visitando unas áreas y luego se trasladada a un país donde las vacunas para fiebre amarilla o cólera son opcionales, éste necesitará estas inmunizaciones.

Es necesario conocer los requisitos de entrada para cada país individual en el itinerario. Esto está en resumen en publicaciones tales como: Health Information for

International Travel" 1978. Para el viajero norteamericano no hay requisitos establecidos cuando visita Europa, Canadá, Méjico y el Area del Caribe, con la excepción de haber ocurrido un brote de viruela, cólera o fiebre amarilla en una de las áreas. La mayor parte de los países que están en su itinerario requerirán un certificado para viruela. Un certificado de fiebre amarilla será exigido en algunos países de Europa, Méjico y el Caribe, pero no en Canadá. Un certificado de cólera será requerido solamente en algunos países de Europa. La vacunación debe ser administrada bajo supervisión estricta de cualquier médico con licencia. La autenticación de los certificados es necesaria y puede obtenerse

en cualquier ciudad vía el Depto. de Salud. Las vacunas en contra de fiebre amarilla deben de ser administradas oficialmente por lo que se conoce como centros de vacunación de fiebre amarilla y el certificado debe de estar validado por uno de estos centros. Los médicos que administran las vacunas a los viajeros deben enfatizar que los certificados de inmunización internacional deben de ser autenticados para ser aceptados por las autoridades de cuarentena. De no tener la validación esto resultará en que el viajero sea revacunado o retenido en cuarentena. Algunos países no requieren certificados internacionales de vacunación para infantes menores de 13 meses de edad. Se debe de cotejar las excepciones para cada país en específico. Si el médico opina que la vacunación no debe de llevarse a cabo por razones médicas, al viajero debe entregársele un documento firmado y fechado en papel oficial por el médico explicando las razones. Las vacunas de viruela y fiebre amarilla se pueden administrar simultáneamente en lugares distintos sin temor a que se afecte la efectividad individual de cada vacuna. Se recomienda que todos los ciudadanos norteamericanos

americanos que estén planeando viajes internacionales tengan completados todas sus inmunizaciones de rutina con sus refuerzos los cuales deben de tenerlos para su protección en los Estados Unidos. Estas inmunizaciones son todas las que son usualmente necesarias para los patrones usuales de viaje en Europa, Canadá, Méjico y el Caribe. Para viajeros en otras áreas del mundo, el médico debe de preguntar al viajero cuanto tiempo estará en estas áreas y los estilos de vida que llevará allí. Un visitante a India que pasará su tiempo en Nueva Dehli, Acra y Bombay es muy diferente a una persona que pasará su tiempo o tiempos prolongados en villas en circunstancias donde el estilo de vida es muy diferente al de las ciudades y muy parecido al del ciudadano nativo. Es altamente cuestionable si la persona en la primera instancia necesita cualquier otro tipo de inmunización además de las que hemos mencionado. Los riesgos de esta persona de desarrollar tifoidea, plaga y tifus son extremadamente remotas y estas vacunas proveen protección relativa y transitoria solamente. Estas vacunas no se deben usar rutinariamente. Es mucho más sabio para el viajero el concentrar su atención en la profilaxis de malaria y tomar las precauciones necesarias para asegurar que su ingestión de líquido sea saludable. Si el viajero pasará tres meses o más en áreas tropicales o países en desarrollo donde hepatitis A es común, se debe de administrar globulina inmune sérica, dos mililitros para adultos quedándose tres meses y cinco mililitros repetidos cada cuatro a seis meses para personas que se queden por períodos más largos.

Hemos presentado a ustedes un resumen del status de vacunación para los adultos y recomendaciones específicas de cómo deben de vacunarse estas personas.

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BRIEF COMMUNICATION:

ARE WE ORDERING UNNECESSARY AMYLASE STUDIES?

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Summary: The clinical indication for requesting serum amylase studies in 56 instances was analyzed. It was found to be justified in only 24 (43 percent). The results were normal in 45 cases (80 percent). Furthermore, the degree of abnormality in nine was not clinically significant, thus only two results could be considered truly abnormal in relation to the possibility of acute pancreatitis. A plea is made for physicians to be more conscientious when ordering laboratory tests, serum amylase in particular, since it has a very low yield.

Resumen: La indicación clínica para justificar la solicitud de un estudio de amilasa, se analizó en 56 ocasiones. Se encontró justificada solo 24 veces (43 por ciento). Los resultados fueron negativos en 45 casos (80 por ciento). En nueve de los positivos, el grado de anormalidad fue tan bajo que se hace prácticamente inservible para la confirmación de una sospecha de pancreatitis aguda. Se insta al médico a que busque ayuda en el laboratorio solo en aquellos casos que tiene una razón clínica de peso, sobre todo

cuando se trata de la determinación de amilasa en el suero ya que el rendimiento de esta prueba es notoriamente bajo.

Introduction

There is no doubt that the practice of medicine has become progressively, and alarmingly, dependent on technology, both in the diagnostic and therapeutic fields. To a certain extent, history-taking has been substituted by test-requesting and, not infrequently, hospital records show a Doctor's Orders page filled with laboratory requests while sketchy, superficial and insufficient information is scribbled on the page of History of Present Illness. It appears that, as technological information becomes more readily available, the physician relies less on the medical history, and reduces this task to a careless and meaningless one.

One of the tests that has caught my attention as being often unnecessarily used, is the Serum Amylase. Having this in mind, *all* serum amylase studies that were requested by the Admission and Emergency Room areas of the VA Hospital between June 1 and December 31, 1979 were reviewed. It was discovered that out of a total of 489 determinations,

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TABLE I

Guidelines for Justification of Amylase Test

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1. *Abdominal symptoms related to excessive alcohol intake.*
 2. *Abdominal trauma.*
 3. *Cholelithiasis suspected to cause recurrent pancreatitis.*
 4. *History of chronic pancreatitis.*
 5. *Unexplained abdominal pain with or without referral to the back.*
 6. *Unexplained persistent or recurrent nausea and vomiting associated with epigastric tenderness.*
 7. *Unexplained signs of peritoneal irritation.*
 8. *Unexplained superior abdominal mass.*
-

345 (70.6 percent) were normal. Any value above the maximum of the normal ranges was considered abnormal. The ones used at our laboratory are as follows: 1- Manual Procedure - 45-200 Dye Units; 2- A. C. A. Procedure (automated) - 5-81 International Units.

In view of this finding, a prospective study was designed to determine the conditions under which this test was being ordered. In other words, the purpose was to find out whether the tests requested were medically justified.

Materials and Methods

Every morning the laboratory Chief Technologist would provide us with the results of the tests performed in the Admission and Emergency Room areas during the previous 24 hours. The clinical record, corresponding to the visit when the serum amylase was requested, was reviewed and analyzed in the light of pre-established criteria (Table I) for justification of the order. A one week follow-up was carried

out in the hospitalized cases to discover any change in the course of the patient's clinical picture that would support the ordering of the test. As a rule, these tests were ordered by interns and residents of the Departments of Medicine and Surgery. Occasionally, members of the Staff participated in these decisions.

The guidelines established for justification of the order were purposely made ample to cover a wide range of conditions where the amylase test might be indicated. Absence of *all* of them from the clinical record was the measurement taken to declare the requested test as unjustified. The normal ranges used were the ones previously stated in the introduction.

Results

Fifty-six (56) tests were requested between March 21 and April 17, 1980. Using the routine standards referred above, 45 (80 percent) were reported normal. As a matter of fact, only two cases, of the eleven where the result of the test was above normal, were

TABLE II

Physicians		Tests *	Indicated	Normal	Abnormal (units) **
1	(R.)	2	1	2	
2	(S.)	2	1	2	
3	(R.)	4	1	3	1(324)
4	(H.)	1	1		1(154)
5	(G.)	2	1	2	
6	(R.)	2	1	2	
7	(P.)	4		4	
8	(M.)	2	1	2	
9	(L.)	3	2	3	
10	(G.)	3	1	2	1(97)
11	(G.)	2		2	
12	(A.)	1		1	
13	(F.)	2	1	1	1(91)
14	(H.)	4	1	3	1(90)
15	(P.)	1		1	
16	(A.)	1	1		1(1,400)
17	(I.)	2		1	1(127)
18	(B.)	4	2	4	
19	(R.)	1	1		1(95)
20	(R.)	1	1	1	
21	(S.)	4	2	4	
22	(O.)	1		1	
23	(T.)	1			1(125)
24	(P.)	1		1	
25	(R.)	1	1	1	
26	(G.)	2	2	1	1(210)
27	(T.)	1	1	1	
28	(A.)	1	1		1(164)
Totals		56	24	45	11

* - There is one test per case.

** - Result from test ordered by Physician No. 26 was obtained through the manual procedure; all others through A. C. A.

Twenty-eight (28) different physicians were involved.

associated with recognizable disease: one had acute pancreatitis (1,400 units) and the other was diagnosed mesenteric thrombosis at laparotomy (324 units).

In 32 of the 56 instances (57 percent), nowhere in their clinical records appeared written evidence of any one of the eight (8) pre-established guidelines (Table I) to justify the request of the test. In three of the eleven cases where the results were abnormal (above the routine maximal ranges), the medical record did not reveal any written evidence that would satisfy any one of the pre-established criteria. This practice was not the reflection of just a few physicians. Again, according to the guidelines established, out of a total of 28 physicians who ordered the amylase test, 18 did not provide information in the clinical records that would justify the request. It is also interesting to note that in six instances, the order requesting a serum amylase determination did not appear in the chart.

The studies also suggest the existence of an erroneous notion that diarrhea is a constituent of the syndrome of *acute* pancreatitis, since the serum amylase was requested in four cases where diarrhea was a prominent symptom in the acute episode under investigation.

Comments and Conclusions

These findings definitely suggest that

these tests were ordered with insufficient clinical justification. What makes matters worse is that patients are sometimes kept waiting in the Emergency Room pending the result of a serum amylase determination which in the end is not going to alter the physician's decision, as in the majority of the cases the test is not indicated and in a greater number of them it is normal. Furthermore, the yield in this test is so low even in cases where it is clinically justified, that one is tempted to conclude that there is little merit to its use.

If this situation exists in relation to a specific study that is requested only in response to a given sign or symptom, one wonders what may be happening with simpler tests which are available for "routine" use. These findings are presented in the hope that physicians become more conscientious with the use of laboratory studies and order them *only* when there is a sound medical reason to do so.

Acknowledgment

I want to express my gratitude to Mr. David González, Chief Technologist, for his cooperation in providing all the pertinent laboratory information.

Progreso Terapéutico: LAS TETRACICLINAS

Héctor F. Gorbea, MD y Carlos H. Ramírez Ronda, MD, FACP

Resumen: Las tetraciclinas son un grupo de antibióticos bacteriostáticos de amplio espectro cuyo uso puede ser variado. Son antibióticos de primera elección en infecciones primarias del tracto urinario en adultos varones, causadas por microorganismos susceptibles. Son efectivos en el manejo de uretitis no específica y como tratamiento alternativo de sífilis y gonorrea. Son efectivos en infecciones causadas por *Mycoplasma pneumoniae* y pueden utilizarse en exacerbaciones agudas de bronquitis crónica. Algunas de las formas de las tetraciclinas como doxiciclina pueden utilizarse en pacientes con insuficiencia renal.

Los efectos secundarios de este grupo de antibióticos son variados. Su uso está muy limitado en niños y mujeres embarazadas. Infecciones y superinfecciones ocurren con frecuencia. Demetilclortetraciclina y otras tetraciclinas se asocian a reacciones de fotosensitividad.

Estos antibióticos son efectivos y tienen su lugar limitado y específico en el armamentario del médico.

Introducción

Las tetraciclinas son antibióticos de amplio espectro, originalmente aisladas de cultivos de algunas especies del hongo *Streptomyces*. Actualmente contamos con varios compuestos derivados del núcleo de tetraciclina, todos con estructuras moleculares similares y espectro de actividad parecida. La primera tetraciclina fue aislada en 1948 de *Streptomyces aureofaciens*, a ésta se le denominó clortetraciclina. Oxitetraciclina fue derivada de cultivos de *Streptomyces rimosus* unos años más tarde. Estudios de la estructura de clortetraciclina resultaron en la preparación de demetilclortetraciclina así como de otros agentes similares que han sido derivados de hongos o sintetizados químicamente. En la actualidad el grupo de las tetraciclinas incluye a la metaciclina, doxiciclina y minociclina, además de los mencionados (1).

Modo de Acción y Farmacología

El modo de acción de las tetraciclinas es inhibiendo la síntesis de proteínas en las bacterias. Específicamente, estos antibióticos se adhieren a las subunidades 30S de los ribosomas bacterianos inhibiendo la unión entre el ácido ribonucleico de transferencia y los ribosomas.

Las tetraciclinas se absorben en todo el tracto gastrointestinal. Esta absorción

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no es completa ya que siempre hay una proporción de la dosis del antibiótico que no se absorbe, la proporción aumenta con dosificaciones mayores del antibiótico. Se han considerado principalmente dos factores para explicar esta absorción incompleta. Primero, la solubilidad, la cual es mayor en agua pero menor en medios alcalinos o neutrales, en estos medios estos antibióticos tienden a precipitarse. Segundo, las tetraciclinas se combinan con metales divalentes, especialmente con calcio, el cual está presente en concentraciones mayores en el tracto gastrointestinal. Es común que sales de fosfato se incluyan en las cápsulas de tetraciclinas ya que esto aumenta la absorción al combinarse el fosfato con el calcio.

Después de la absorción las tetraciclinas penetran bien en las cavidades pleurales, peritoneales y sinoviales, y cruzan las membranas placentarias entrando en la circulación fetal. Algunas de las tetraciclinas aparecen en secreciones glandulares, encontrándose en concentraciones bajas en lágrimas y saliva. Las tetraciclinas penetran al líquido cefalorraquídeo en concentraciones de alrededor del diez por ciento de las concentraciones encontradas en la sangre. Estos agentes se depositan en huesos y dientes. Todas las tetraciclinas se adhieren a proteínas plasmáticas en cantidades variables, desde veinte y veinticuatro por ciento para oxitetraciclina y tetraciclina respectivamente, hasta cuarenta y siete por ciento para clortetraciclina.

Todas las tetraciclinas se excretan en mayor o menor grado por la vía renal a través del mecanismo de la filtración glomerular. El veinte por ciento de una dosis administrada por vía oral se excreta en la orina en veinticuatro horas, mientras que más del cincuenta por ciento de una dosis de tetraciclina administrada por vía parenteral endo-

venosa se excreta en la orina en el mismo tiempo. Una segunda vía de excreción es la vía biliar. En la bilis la concentración del antibiótico puede llegar a concentraciones de diez a veinte veces mayores que en la sangre. Doxiciclina se excreta mayormente en la bilis y hay evidencia de que se excreta directamente por el tracto gastrointestinal, este último puede ser el mecanismo principal de excreción en pacientes en fallo renal. Las tetraciclinas excretadas en la bilis se reabsorben parcialmente en el intestino y el resto aparece en las heces. Solamente una pequeña fracción de la tetraciclina se inactiva en el hígado, por lo cual se depende principalmente de la excreción renal y biliar para su eliminación. Una excepción a esto es la doxiciclina, en la cual aproximadamente el cincuenta por ciento se inactiva en el cuerpo. Si tomamos en consideración la inactivación en el hígado de doxiciclina y su excreción eficiente por mecanismos no renales podemos comprender por qué esta tetraciclina no se acumula en pacientes en fallo renal y es la tetraciclina de elección en este tipo de pacientes cuando una tetraciclina está indicada.

Organismos susceptibles:

La mayoría de las bacterias gram-positivas son susceptibles a las tetraciclinas. Organismos como *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Viridans streptococci*, *Streptococcus fecalis* y los estreptococos anaeróbicos son susceptibles a las tetraciclinas. Bacilos gram-positivos como *Bacillus anthrax*, *Clostridium tetani*, *Clostridium perfringens* y *Listeria monocytogenes* son también susceptibles a las tetraciclinas. Es importante enfatizar que a pesar de que como grupo estas bacterias son susceptibles desde

el punto de vista microbiológico muchas de éstas pueden desarrollar resistencia a las tetraciclinas, y por lo tanto la susceptibilidad de grupo no necesariamente significa que es el antibiótico de elección. Los estafilococos son algunos de los microorganismos que desarrollan resistencia a estos antibióticos fácilmente, requiriendo pruebas de susceptibilidad cuando las tetraciclinas son utilizadas en infecciones por estos microorganismos. Las tetraciclinas también actúan en contra de microorganismos gram-negativos como *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Salmonella* y *Shigella*. *Serratia marcescens* y *Proteus* son usualmente resistentes. A pesar de que *Salmonella* y *Shigella* comunmente son susceptibles a las tetraciclinas en pruebas *in vitro*, estas drogas usualmente no son efectivas en el tratamiento de infecciones por estos organismos. Otras bacterias gram-negativas también son susceptibles a las tetraciclinas, éstas incluyen el meningococo, el gonococo, *Haemophilus influenzae*, *Vibrio cholerae*, *Francisella tularensis*, *Brucella* y *Yersinia*. *Pseudomonas aeruginosa* es invariablemente resistente.

A pesar de que como grupo los bacilos gram-negativos arriba mencionados son susceptibles a las tetraciclinas, muchas cepas de estos son resistentes. Si se piensa utilizar una tetraciclina para tratamiento de una infección causada por un microorganismo gram-negativo, debe de conocerse la susceptibilidad de éste a la tetraciclina a utilizarse.

Treponema pallidum, el agente causante de la sífilis, *Mycoplasma pneumoniae*, las especies de *Actinomyces*, las *Rickettsias* y las *Chlamidias* también son susceptibles a las tetraciclinas.

Dosificación:

Las tetraciclinas usualmente se ad-

ministran por la vía oral. Las dosis de tetraciclina, oxitetraciclina y clortetraciclina es de 25 mg a 40 mg por kilogramo de peso, dividido en cuatro dosis diarias, para niños. Para los adultos, la dosificación es de 250 mg cada seis horas o de 500 mg cada seis horas en infecciones más serias.

Demeticlortetraciclina se administra en niños en dosificación de 12 mg por kilogramo de peso dividido en dos o cuatro dosis diarias y metaciclina en dosificación de 10 mg por kilogramo de peso dividido en dos a cuatro dosis diarias.

La dosificación usual de doxiciclina para los adultos de 200 mg el primer día de tratamiento, seguido de una dosis de mantenimiento de 100 mg por día. En infecciones severas se puede aumentar a 100 mg cada doce horas. Para niños, doxiciclina se administra en dosis de 4.4 mg por kilogramo de peso dividido en dos dosis iguales el primer día de tratamiento, ésto es seguido de 2.2 mg por kilogramo de peso en una sola dosis diaria. Minociclina se administra en adultos en una dosis de 200 mg. seguido de 100 mg cada doce horas.

Las tetraciclinas también se pueden administrar por vías endovenosas o intramusculares. Tetraciclina y oxitetraciclina se administran en dosis de 0.5 gm a 1.0 gm diario endovenoso, nunca debe de excederse una dosis de 2.0 gms por día. El uso endovenoso de tetraciclina causa frecuentemente tromboflebitis. El uso intramuscular de tetraciclina y oxitetraciclina es en una dosificación de 100 mg cada ocho a doce horas. Doxiciclina se administra en dosis de 100 mg una o dos veces al día endovenosamente, diluido en 200 mililitros de líquido para administrarse en 15 minutos. Minociclina se puede administrar en dosis de 200 mg inicialmente seguido de 100 mg cada doce horas, ésto se debe dividir en 500 o 1,000 mililitros de líquido endove-

noso. El uso de tetraciclinas parenterales debe ser limitado y para indicaciones específicas.

Es importante notar que las tetraciclinas no deben usarse en pacientes en fallo renal pues estas drogas se acumulan en dichos pacientes si se administran en la dosificación usual y también pueden contribuir a aumentar el deterioro de la función renal (2, 3). En pacientes con enfermedad hepática las tetraciclinas deben administrarse con cautela pues tienden a acumularse y asociarse con deterioro de la función hepática. El uso de tetraciclinas en el embarazo y en niños debe ser muy limitado y en circunstancias especiales cuando no pueda utilizarse otro agente.

Toxicidad:

Las tetraciclinas pueden causar síntomas de irritación gastrointestinal, siendo comunes: náusea, vómitos, diarreas y malestar epigástrico cuando estos antibióticos se administran por vía oral. Estos síntomas usualmente desaparecen cuando se discontinúa el uso de la tetraciclina y son bastante frecuentes. Los síntomas gastrointestinales se pueden aliviar si las tetraciclinas se administran con comida, con excepción de leche, y antiácidos que no contengan aluminio, magnesio ni calcio. Cuando se administran las tetraciclinas se puede encontrar infecciones secundarias por *Candida albicans* y organismos gram-negativos como *Proteus* y *Pseudomona aeruginosa*. Dos complicaciones raras son la enterocolitis pseudomembranosa estafilococcica y la colitis pseudomembranosa no estafilococcica. Estas condiciones requieren un manejo agresivo y apropiado (4).

Complicaciones de poca frecuencia ocurren, como son las reacciones de hipersensitividad y de fotosensitividad, particularmente

en pacientes usando demeticloretetraciclina, los cuales pueden desarrollar una erupción en áreas expuestas a la luz solar. Las tetraciclinas también pueden causar una decoloración amarillenta de los dientes (5). Esto puede ocurrir en niños de madres que recibieron tetraciclinas durante el embarazo pues estas drogas cruzan la placenta, por lo tanto uno no debe de usar tetraciclina durante el embarazo (6). La deposición de tetraciclina en los huesos de infantes pueden producir una inhibición del crecimiento óseo, esta inhibición desaparece al discontinuar el tratamiento con tetraciclina sin dejar efectos permanentes en los huesos, más por este efecto las tetraciclinas no deben utilizarse en los niños.

Las tetraciclinas pueden producir daño hepático, necrosis grasa aguda, particularmente cuando se administran en dosis endovenosas en exceso de 2 gramos diarios, y particularmente en mujeres embarazadas. En estos casos de mujeres embarazadas se deben usar las tetraciclinas solo cuando todos los otros antibióticos están contraindicados y usando un seguimiento cuidadoso de la función hepática (7, 8).

Las tetraciclinas también pueden causar toxicidad a los riñones. En pacientes en fallo renal, al administrársele tetraciclinas, se puede observar un aumento en el deterioro de la función renal con aumentos en la urea y creatinina sérica (9, 10). Probablemente la causa principal de esta complicación sea el efecto antianabólico de estos antibióticos al inhibir la síntesis de proteínas (11).

El tratamiento con tetraciclinas por largo tiempo puede causar deficiencias de vitaminas, particularmente de vitamina C, cuya excreción mínima aumenta al usar estos antibióticos. Si se administran en dosis altas endovenosas, las tetraciclinas pueden producir problemas de coagulación al modificar los factores de coagulación y prolongar el tiempo

de protrombina. Minociclina en particular puede causar debilidad, mareos, náusea y vértigo, este efecto secundario es de suma importancia el conocerlo. Estos efectos se pueden ver al segundo o tercer día de tratamiento y es reversible al discontinuar el antibiótico.

Uso de las tetraciclinas:

Las tetraciclinas son agentes efectivos en el tratamiento de infecciones del tracto urinario, especialmente en los episodios iniciales. El agente etiológico en estos casos es usualmente *Escherichia coli*, y las concentraciones de tetraciclinas en la orina son bien altas, muy por encima de la concentración mínima inhibidora.

Las tetraciclinas se usan frecuentemente en el tratamiento de infecciones respiratorias, especialmente en exacerbaciones agudas de bronquitis crónica. Estos antibióticos son efectivos en el tratamiento de pulmonías causadas por *Mycoplasma pneumoniae* (12, 13).

Las tetraciclinas también son efectivas en el tratamiento de brucelosis, aunque para casos severos o prolongados se debe de utilizar en combinación con estreptomycin. Colangitis y colecistitis agudas pueden ser tratadas con las tetraciclinas, si el microorganismo causante es susceptible a estos antibióticos y si no hay obstrucción en el tracto biliar. Tetraciclina por vía oral, junto con corrección de la deshidratación, constituyen el tratamiento efectivo de la cólera. Las tetraciclinas se pueden usar para propósitos profilácticos durante epidemias de cólera.

Las tetraciclinas son efectivas en el tratamiento de infecciones por *Rickettsia*, *Borrelia recurrentis* (fiebre ondulante), en tularemia y psitacosis. Las tetraciclinas se usan en el tratamiento de gonorrea como al-

ternativas al uso de la penicilina G (14, 15, 16). Usualmente se recomienda un curso de cinco días con tetraciclina, con una dosis de 500 mg cada seis horas para hombres y para mujeres. Las tetraciclinas son los agentes más efectivos en el tratamiento de la uretritis no específica, donde se consideran las Clamidas como posibles agentes etiológicos (17). También se usan como alternativa terapéutica a la penicilina G en el tratamiento de sífilis en una dosis de 500 mg cuatro veces al día por 15 días para la sífilis primaria, secundaria o latente de menos de un año y por 30 días para sífilis de más de un año de duración (18).

Melioidosis causada por *Pseudomona pseudomallei* se puede presentar como una pulmonía subaguda o como una septicemia fulminante; las tetraciclinas en dosis altas han probado ser efectivas en ocasiones contra este microorganismo. En el cuadro septicémico de melioidosis las tetraciclinas deben de usarse en combinación con otras drogas como cloranfenicol o novobiocina. Las tetraciclinas en dosis bajas, 250 mg diarios, han probado ser de beneficio para pacientes con acné severo. Finalmente las tetraciclinas cuando se usan en combinación con quinina han probado ser efectivas en el tratamiento de malaria por *Plasmodium falciparum* resistentes a cloroquina (19, 20). Un uso reciente que se le ha dado a doxiciclina es en la profilaxis de diarreas del viajero (21), se demostró que el uso de 100 mg de doxiciclina fue efectiva en prevenir la diarrea del viajero. Aunque efectivo, el uso rutinario puede seleccionar cepas resistentes y crear problemas epidemiológicos globales, por esta razón no endosamos el uso rutinario profiláctico en diarrea del viajero. El viajero si es cuidadoso en su ingestión de alimentos usualmente no se infectara con *E. coli* entero-toxigénico.

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CONTESTACIONES A MEDI-QUIZ

I. 1. b

2. a

3. d

4. c

II. 1. c

2. e

3. b

4. a

5. a

6. a. 4

b. 2

c. 4

INFECCION POR TUBERCULOSIS EN LOS ESTUDIANTES DE MEDICINA DEL NIVEL PRECLINICO

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Resumen: Se hicieron pruebas de tuberculina con derivado protéico purificado, 5 unidades, en grupos comparables de estudiantes de medicina de Puerto Rico hace 15 años y en el 1979. Las tasas de infección por tuberculosis fueron de 38 por ciento en el 1964 y 4 por ciento en el 1979. La reducción en las tasas de infección fue de 88 por ciento durante el período del estudio. Esta fue comparable a la reducción de la morbilidad por tuberculosis (de 82 por ciento) durante ese mismo período en Puerto Rico.

Se recomienda que los facultativos y los estudiantes de medicina en sus años clínicos se hagan la prueba de la tuberculina anualmente y que se les administre la quimioprofilaxis con isoniácida a los que tienen el viraje tuberculínico de negativo a positivo.

Summary: Tuberculin tests (PPD 5 TU) were

performed in comparable groups of Puerto Rican medical students fifteen years ago and in 1979. Tuberculosis infection rates were found to be 38 percent in 1964 and 4 percent in 1979. This represented an 88 percent reduction of infection rates during the period of study. This was comparable to a reduction in tuberculosis morbidity of 82 percent in Puerto Rico during the same period.

It is recommended that physicians and medical students in their clinical years be tuberculin tested annually and that isoniazid chemoprophylaxis be administered to converters from negative to positive.

Introducción

La reacción a la prueba de la tuberculina es un instrumento de pesquisa epidemiológica de la tuberculosis que permite medir la magnitud del problema en una comunidad incluyendo la tasa anual de infección en la misma. La reacción a la prueba de la tuberculina es, además, la base para ubicar al individuo en la nueva clasificación de la tuberculosis (1).

El propósito de este trabajo fue analizar en el año 1979 las categorías O y II en nuestros estudiantes de medicina, determinar en dicho grupo la tasa de infección anual por tuberculosis durante los últimos 23 años, com-

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Presentado ante la 77 Reunión Anual de la Asociación Médica de Puerto Rico, 10 de noviembre de 1979.

TABLA I

Infección por Tuberculosis en los Estudiantes de Medicina del Nivel Preclínico
en Puerto Rico
1964 - 1979

Sujetos	Edad Promedio	Porcentaje de Reacciones al PPD 5 TU (mm de induración)			Tasa Anual de Infección
		0	1-9	10 o más	
Estudiantes de Medicina y Odontología - 1964 Núm. 272	23 años	43 por ciento (118/272)	19 por ciento (51/272)	38 por ciento (103/272)	1.6
Estudiantes de Medicina 1979 Núm. 161	23 años	86 por ciento (139/161)	9 por ciento (15/161)	4.3 por ciento (7/161)	0.19

parar la situación del 1979 con la del 1964 y hacer algunos comentarios alusivos a los hallazgos.

Los estudios de la infección por tuberculosis presentados en este trabajo sirvieron los siguientes propósitos adicionales: (1) adiestrar los estudiantes de medicina al finalizar su segundo año en los aspectos epidemiológicos y de salud pública de la infección tuberculosa; (2) iniciar en dichos estudiantes la práctica de hacerse la prueba de la tuberculina como una medida importante del mantenimiento de su salud y, a la vez, estimularlos a emplear el procedimiento en sus pacientes; (3) establecer un método de vigilancia del control de la tuberculosis en Puerto Rico.

Materiales y Métodos

Se hizo la prueba de la tuberculina emplean-

do el derivado protéico purificado en dosis de 5 unidades. La misma se aplicó y se midió usando métodos estandarizados descritos previamente (2).

En el 1964 se utilizó el derivado protéico purificado (PPD S), en dosis de 5 unidades, elaborado y distribuido por Salud Pública Federal ya diluido y rotulado con fecha de vencimiento. En el 1979 se utilizó el derivado protéico purificado, PPD, ya diluido y estabilizado con el detergente "Tween 80" (Parke Davis) en la dosis intermedia de cinco unidades. Con la piel en tensión se introdujo la aguja transversalmente, superficialmente, intracutánea, de manera que al inyectar la cantidad de 0.1 ml del fluido se formara una vesícula de alrededor de 6 mm de diámetro. La lectura de la prueba se hizo de 48 a 72 horas después de la inyección. Se midió la reacción con una regla marcada en milímetros. Cuando había reacción se midió la pápula palpándola transversalmente, en la misma dirección en que fue inyectada la tuberculina anotándose el resultado en milímetros.

La muestra de 1964 incluyó, principalmen-

TABLA II

Disminución de la Infección en los Estudiantes de Medicina del Nivel Preclínico
Comparada con la Morbilidad y Mortalidad por Tuberculosis 1964 a 1977-79

Año	Infección (Tuberculina Positiva)		Morbilidad *		Mortalidad *	
	Puerto Rico		Casos/ 100,000 habitantes		Casos/ 100,000 habitantes	
	Positivos/total	Por Ciento	P. R.	E. U.A.	P. R.	E. U.A.
1964	103/272	(38 por ciento)	65.0	26.6	19.6	4.3
1977					6	1.4
1978			11.7	13		
1979	7/161	(4.3 por ciento)				
Disminución		-88.5 por ciento	-82 por ciento	-51 por ciento	-69 por ciento	-67 por ciento

* Fuentes : U. S. Department of Health Education & Welfare/PHS/MMWR Annual Summary 1978, Vol. 27, pp. 3, 5, 13; No. 54, 1979.

Informe Anual de Estadísticas Vitales del Departamento de Salud de Puerto Rico, 1965. Programa de Control de Tuberculosis, Departamento de Salud de Puerto Rico, Informes de Estadísticas.

te, estudiantes de medicina y algunos de nuestra Escuela de Odontología. La del 1979 incluyó principalmente estudiantes de medicina de la Universidad de Puerto Rico y algunos de la Universidad Católica de Ponce. En todos los grupos la edad promedio de los sujetos fue de 23 años. Los estudiantes no habían comenzado la fase clínica de sus estudios. Las reacciones de 10 mm o más fueron consideradas positivas y evidencia de infección por tuberculosis.

Resultados

Los resultados se presentan en la Tabla I. En 1964, 103 de 272 (el 38 por ciento)

de los estudiantes presentaron reacciones positivas a la prueba de la tuberculina ubicándolos en la categoría II de la clasificación de tuberculosis. Esta cifra bajó a 7 reacciones positivas en 161 estudiantes (4.3 por ciento) en el 1979. Al dividir el porcentaje de positivos por la edad promedio de los sujetos, se encontró que la tasa de infección anual bajó de 1.6 por ciento en el 1964 a 0.19 por ciento en el 1979. La disminución en la tasa de infección durante los pasados 15 años fue de 88 por ciento. Las cifras coinciden con el escaso número de niños con reacciones positivas a la tuberculina observados en los años recientes en el Hospital Universitario de Ni-

TABLA III

Infección por Tuberculosis en los Médicos de California por Especialidad *

<i>Medicina Interna</i>	<i>14 por ciento</i>
<i>Cirugía</i>	<i>9.1 por ciento</i>
<i>Pediatría</i>	<i>9.6 por ciento</i>
<i>Obstetricia-Ginecología</i>	<i>6.8 por ciento</i>
<i>Ortopedia</i>	<i>6.2 por ciento</i>
<i>Radiología</i>	<i>4.9 por ciento</i>
<i>Siquiatría</i>	<i>4.0 por ciento</i>

* Referencia (4), Barrett-Connor, E.

ños pero estos datos no han sido recopilados. También coinciden con las tasas de infección informadas en la población general por el Departamento de Salud en el 1979 en personas de 14 a 24 años de edad las cuales fueron de 4 por ciento (3). El porcentaje de la reducción en la infección se acerca al porcentaje de reducción en la morbilidad por tuberculosis en Puerto Rico desde el 1964 (Tabla II). En los Estados Unidos durante el mismo período la morbilidad disminuyó menos que en Puerto Rico (51 por ciento) y la mortalidad en forma comparable a Puerto Rico (67 por ciento) (Tabla III).

Discusión

Los datos encontrados en jóvenes

estudiantes de las ciencias médicas de Puerto Rico demuestran que la infección por tuberculosis ha disminuído considerablemente en los últimos quince años. No se pueden explicar las disminuciones por cambios en los niveles sociales o económicos de los estudiantes. Durante este período los criterios socioeconómicos de admisión a la Escuela de Medicina no han variado y el coste de los estudios se ha mantenido casi inalterado. La matrícula anual se ha mantenido cerca de \$500 y se le ha continuado la ayuda económica para los estudiantes necesitados. El hecho de que la morbilidad ha disminuído en forma comparable a la infección está de acuerdo con el concepto epidemiológico actual de que la mayoría de los casos de tuberculosis surge de personas ya infectadas, o sea, las que ya tienen la tuberculina positiva. Es posible

que la muestra no represente fielmente la población general de Puerto Rico. Pero el hecho de que las cifras de positividad en los estudiantes de medicina se acercan a las encontradas por el Departamento de Salud en grupos de la población general durante el mismo año sugiere que los datos encontrados no se alejan de la realidad puertorriqueña.

A pesar del optimismo que se desprende de las cifras de morbilidad de Puerto Rico, todavía no se pueden aceptar dichas cifras sin la debida cautela. La búsqueda de casos en Puerto Rico ha sufrido en años recientes de la insuficiencia de los estudios microbiológicos debida a los problemas que ha tenido el laboratorio de micobacteriología del Departamento de Salud.

Desde el punto de vista de los profesionales de la medicina cabe señalar que las cifras encontradas son las de estudiantes que no han encontrado en la fase clínica de sus estudios y no pueden aceptarse como las que se encontrarían en un grupo de médicos en el ejercicio de la profesión. Esto se ha demostrado en la encuesta de reacciones a la prueba de tuberculina entre los médicos graduados de distintas escuelas de medicina de California en donde la morbilidad por tuberculosis es un poco más alta que en Puerto Rico (4). En estos médicos de California se descubrió que la tasa de infección por tuberculosis era más alta que la de la población general, particularmente en los cinco primeros años después de graduados en los que se encontró que la cifra era de 2.9 por ciento. También se encontró que el riesgo era diferente de acuerdo con la especialidad que éstos ejercieron (Tabla III). Fue más alto en los que practicaban la medicina interna (14 por ciento) y más bajo en los psiquiatras (4 por ciento).

Nuestro estudio se hizo en estudiantes de medicina que no habían empezado

en la fase clínica, en la que empiezan las oportunidades de contagio con tuberculosis. En la fase clínica de los estudios de medicina y después de graduado el estudiante en la categoría O de tuberculosis podría considerarse que se acerca a la categoría I. La categoría O incluye la mayoría de las personas actualmente, los no infectados: o sea, los que tienen reacción negativa a la prueba de la tuberculina; la I incluye las personas en contacto con enfermos tuberculosos contagiosos pero sin infección, o sea, que todavía la reacción a la prueba de la tuberculina es negativa; la II incluye las personas con tuberculina positiva, o sea, los infectados que no están enfermos con tuberculosis; y la III incluye las personas que tienen la enfermedad tuberculosa pulmonar o extrapulmonar.

La manera de evitar tuberculosis ha sido motivo de debate. En las categorías O y I se ha dicho que si el peligro de la infección asciende a más de 1 por ciento por año la vacunación con BCG está indicada. En Puerto Rico los resultados de la vacunación con BCG en niños fueron insatisfactorios y ha sido nuestra política no emplear dicha vacuna (5). Los resultados del ensayo más abarcador del mundo de la BCG en 400,000 adultos de la India son aún más desalentadores que los del estudio en Puerto Rico. Un placebo no fue más eficaz que la BCG para evitar la tuberculosis (6). Aún cuando la BCG fuera eficaz la experiencia en California demuestra que, aunque la infección en los médicos durante los primeros cinco años después de graduados es alta, la misma no sobrepasa la cifra de 1 por ciento por año. En la categoría II se conoce que el tratamiento preventivo con isoniácida es eficaz, particularmente, si se emplea durante el primer año del viraje tuberculínico, o sea, el año durante el cual se conoce que sucedió el cambio de reacción a la prueba de la tuberculina de negativo a positivo. En este año las probabilidades en

las personas recién infectadas de desarrollar tuberculosis activa son de 5 por ciento (7). Los médicos y estudiantes de las ciencias de la salud en la categoría O de la clasificación de la tuberculosis deben hacerse la prueba de la tuberculina una vez al año o con mayor frecuencia. Si la reacción se torna positiva es aconsejable el tratamiento profiláctico con isoniácida en dosis de 300 mg una vez al día por un año (1).

En la población general no estaría indicada la prueba de la tuberculina anualmente ya que el rendimiento de reacciones positivas sería muy bajo, pero sí estaría indicada en las personas de la categoría O con síntomas inexplicables, lesiones pulmonares persistentes o en las que se sospecha contacto con enfermos tuberculosos. En los niños de Puerto Rico deberá hacerse la prueba alrededor de los 13 o 15 meses de edad antes de aplicar la vacuna de sarampión y luego cada 4 o 5 años a menos que vivan en una comunidad de alto riesgo de tuberculosis, tengan síntomas o signos

inexplicables, presenten lesiones pulmonares persistentes o tengan contacto con un enfermo tuberculoso.

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ANGINA PECTORIS WITH NORMAL CORONARY ARTERIOGRAMS

Robert A. Chahine, MD

The syndrome of angina with normal coronary arteriograms has been the subject of intense interest and skepticism since its initial description. The traditional pathogenetic concepts of myocardial ischemia have constantly emphasized the importance of fixed atheromatous coronary artery obstruction. It is therefore no surprise that there would be some resistance to accepting the concept of a myocardial ischemic syndrome occurring in patients with healthy coronary arteries.

In revisiting the syndrome of angina pectoris with normal coronary arteriograms the pragmatist should first realistically examine the appropriateness of the terminology "normal coronary arteriograms" as a reflection of complete anatomic normalcy of the coronary arteries. Coronary arteriograms are considered normal when the major coronary vessels are all seen to be patent and free of any luminal narrowing. Since the anatomy of the secondary branches of the coronary tree is quite variable, total absence of important branches of the major vessels

can go unnoticed and may not be recognized as an abnormality. Also since angiographic resolution has its limitations, cases with minimal nonobstructive luminal irregularities are frequently lumped with normal coronary arteries. In addition there are a number of potential sources of error in the interpretation of coronary angiograms that may lead to the erroneous conclusion of normalcy in spite of the presence of significant disease. These include: 1. Foreshortening of vessels coursing perpendicular to the plane of projection; 2. Flush occlusion of smaller arterial branches; 3. Occlusion of terminal vessels with small lumen, which may not be recognizable; 4. Pseudo interpretation as congenital absence of major branch occlusion; 5. Overlapping of vessels hindering accurate interpretation; 6. Eccentric lesions which may be completely missed if the appropriate projection is not obtained during the study. Although some of these potential sources of misinterpretation of the angiograms may be relatively easy to overcome, there is no question that some of these factors may account for at least a small percentage of the patients with angina and so called "normal coronary angiograms". Therefore any objective analysis of the pathophysiology of the syndrome of angina with normal coronary

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angiograms should keep in mind the contribution of such cases to the total number of patients included in a given study.

The next important problem to consider is the definition of angina itself. Conventionally the term angina is utilized to refer to chest pain syndromes believed to be due to myocardial ischemia. Angina is considered to be classic or typical if the pain satisfies a number of criteria: 1. Retro-sternal location. 2. Oppressive character usually described as crushing weight, constricting or vise-like in nature and referred to by the patient with the clenched fist sign. 3. Specific areas of radiation, mostly the ulnar aspect of the left arm, but also both arms, the jaw, the shoulder, the epigastrium or the back. 4. Tendency of the pain to occur on effort with exacerbation after meals or during cold weather and relief by rest or intake of nitroglycerin. 5. Short duration, usually only a few minutes. 6. Evidence of myocardial ischemia reflected on the electrocardiogram taken during the pain, consisting usually of horizontal or down-sloping S-T segment depression.

There are other types of angina that deviate from classic angina, such as unstable angina, where pains may occur at rest or tend to show a crescendo pattern. Prinzmetal's variant angina is characterized by chest pains occurring mostly at rest with accompanying electrocardiographic S-T elevation instead of the usual S-T depression. The term atypical angina is utilized when some but not all of the above criteria are present. Therefore in general the term angina is considered appropriate as long as the chest pain is believed or known to be secondary to myocardial ischemia. The term chest pain syndrome is broadly utilized to encompass a variable group of cases with some features resembling angina, but where the pain may or may not be related to ischemia. There is unfortunately some con-

fusion about angina with normal coronary angiograms and other chest pain syndromes not related to myocardial ischemia.

Although the pool of patients reported with angina and normal coronary arteriograms may certainly include some patients with coronary abnormalities that are not clearly apparent on the angiograms and probably some patients with chest pain syndromes not related to myocardial ischemia, there is enough evidence supporting the occurrence of true ischemic angina in patients with grossly normal epicardial vessels at angiography. The pathophysiologic mechanisms underlying the occurrence of ischemia in such cases have been the focus of increased attention during the past decade. Research and speculation have jointly resulted in a long list of factors which may be classified into three major groups: (1) Transient mechanical vascular obstruction. (2) Intramyocardial small vessel disease. (3) Physiologic imbalance of the oxygen supply/demand mechanism.

Transient mechanical vascular obstruction may occur as a result of: (a) coronary artery spasm which by definition is a reversible phenomenon produced by constriction of the arterial smooth muscle coat, (b) thrombo-embolic phenomena with subsequent recanalization; platelets are believed to play a major role here, (c) myocardial bridges consisting of muscular bands which overlap the epicardial coronary arteries and may restrict coronary flow mainly in systole; under certain circumstances where the systolic contribution to total coronary flow may become critical the bridges can produce an anginal syndrome, (d) coronary artery dissection.

Of the above factors coronary artery spasm seems to be the most logical culprit in the majority of instances. It is now unquestionably proven that spasm can produce all degrees of ischemia with attending clinical

manifestations. It has been documented in a large number of patients with Prinzmetal's variant angina with or without evidence of significant atheromatous disease. There is also evidence that spasm may play a more extensive role in the broad spectrum of ischemic heart disease. It remains to be proven, however, that spasm can produce clinically recognizable ischemia in vessels that are perfectly normal. Many of the cases of variant angina presented as having normal coronary arteriograms do show minor irregularities, probably secondary to non-obstructive atherosclerotic plaques. These may play a role in triggering the vasospastic phenomenon.

Intramyocardial small vessel disease has frequently been proposed as an explanation for ischemia when no obstruction could be found in the larger epicardial vessels. The presence of small vessel disease has been noted in many conditions including diabetes mellitus; collagen vascular diseases: periarteritis nodosa, systemic lupus erythematosus and progressive systemic sclerosis; infiltrative diseases such as amyloid; connective tissue diseases such as Marfan's or Hurler's syndrome; neuromuscular diseases such as the muscular dystrophies and hematologic diseases such as thrombotic thrombocytopenic purpura or disseminated intravascular coagulation. It should be remembered, however, that obstruction of the larger epicardial arteries may occur in many of these diseases and it would not be easy to find good documentation of small vessel disease in any of these conditions, resulting in an ischemic syndrome in the absence of large vessel involvement. Therefore if small vessel disease accounts for any cases of angina with normal coronary arteriograms, these certainly would constitute a small minority of the total patient population involved.

As to the physiologic imbalance of

oxygen supply/demand mechanisms, an attractive hypothesis was postulated that implies an abnormality of the hemoglobin-oxygen dissociation curve. Although interesting, this abnormality has not been substantiated by any convincing study as a true mechanism accounting for myocardial ischemia in the absence of coronary obstruction. The ventricular hypertrophic diseases such as hypertension, aortic valve disease and hypertrophic cardiomyopathy can produce a physiologic imbalance of the oxygen supply and demand by virtue of the hypertrophy resulting in abnormally large oxygen demand which exceeds the delivering capacity of the coronary vascular bed. However, the majority of patients described as having angina with normal coronary arteries do not have evidence of left ventricular hypertrophy and this mechanism is also not likely to be playing an important role.

It is therefore obvious that many questions related to the syndrome of angina pectoris with normal coronary arteriograms are still waiting for answers. The past decade has witnessed very important progress in our understanding of this syndrome and in our ability to document the ischemia particularly when due to coronary artery spasm. We still do not know, however, if clinically significant spasm may really occur in perfectly normal vessels or whether some mild disease is a prerequisite to serve as a trigger for the spasm; nor do we know the exact or relative role of the other factors proposed to explain the mechanism of angina with apparently normal coronary arteries. Therefore, in revisiting the syndrome of "angina with normal coronary arteriograms" and reviewing our current knowledge and understanding of its underlying mechanisms, one can only reminisce on an observation of Sir Cecil Rhodes, "So little done, so much to do".

GRAPHICS

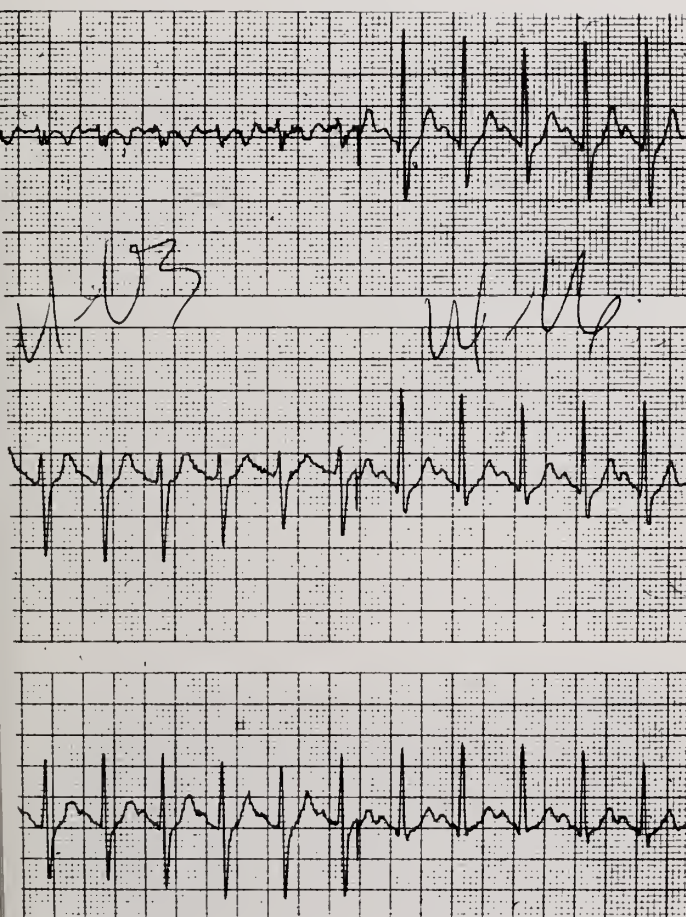


Figure 1a: Exercise electrocardiogram

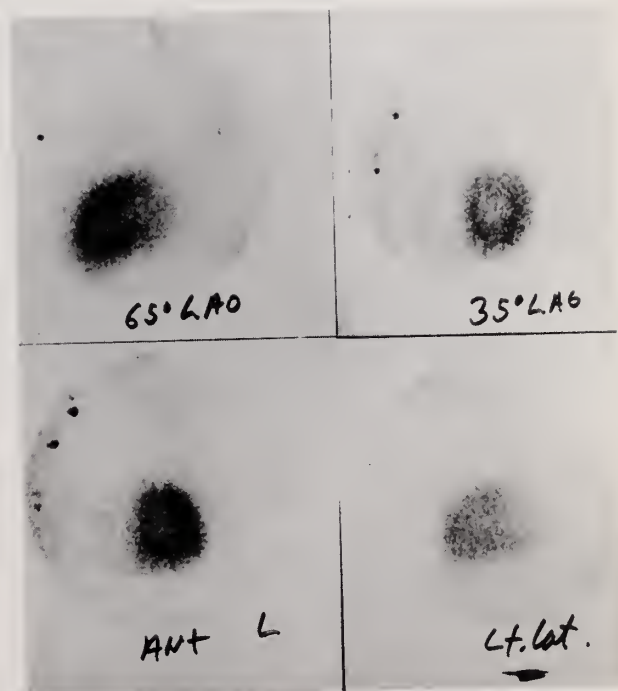


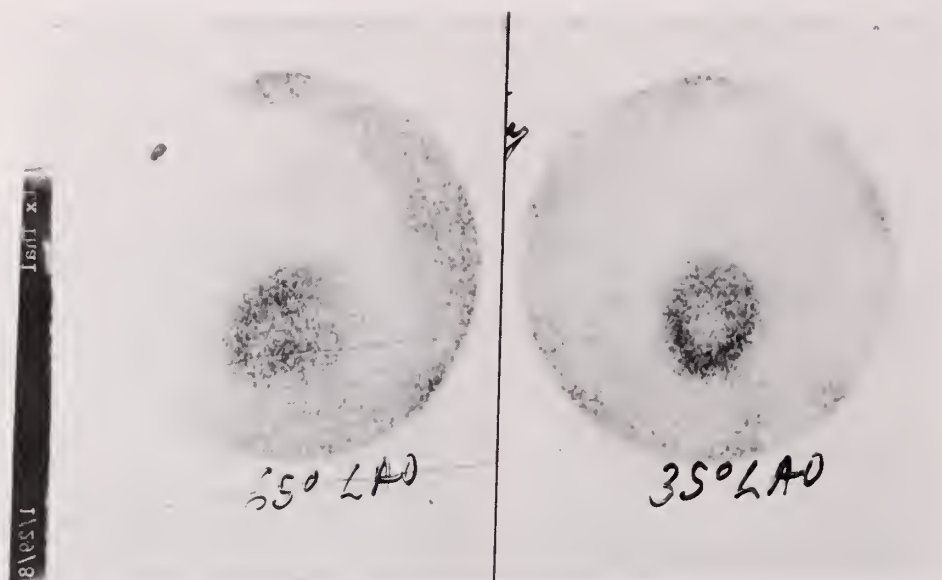
Figure 1b: Exercise ^{201}Tl scan

65° left anterior oblique (top left), 35° left anterior oblique (top right), anterior view (bottom left) and left lateral view (bottom right)

Case 1

This 55-year old male complained about chest pain, unrelated to effort, for the previous six months. There was no history

of dyspnea or orthopnea, but he gave a history of arterial hypertension, and was currently receiving propranolol 20 mg q.i.d. Physical examination disclosed a blood pressure of 160/100 mm Hg, pulse of 78/min regular,

Figure 1c: ^{201}Tl scan delayed images

65° left anterior oblique (left) and 35° left anterior oblique (right)

and unremarkable cardiac examination. The ECG at rest was within normal limits. Myocardial perfusion imaging with ^{201}Tl was obtained in conjunction with a bicycle ergometer test. He exercised for 12 min (150 watts) and achieved a heart rate of 100 percent of that expected for his age group. His

blood pressure rose to 220/120 mm Hg. The test was stopped due to leg fatigue. His exercise electrocardiogram and the myocardial perfusion images are consistent with a) inferior wall myocardial ischemia, b) lateral wall ischemia, c) normal response to exercise.

Case 2

This 57-year old female gave history of chest pain of three months duration. These episodes were not associated with shortness of breath and were unrelated to effort. There was no history of arterial hypertension. Physical examination revealed a blood pressure

of 150/85 mm Hg, pulse 80/min regular, and unremarkable cardiac findings. The ECG at rest showed high voltage in lateral precordial leads without ST segment abnormalities. She underwent a ^{201}Tl myocardial perfusion test after six minutes of ergometer exercise to a level of 90 watts. The blood pressure rose to 220/110 and she achieved a maximal

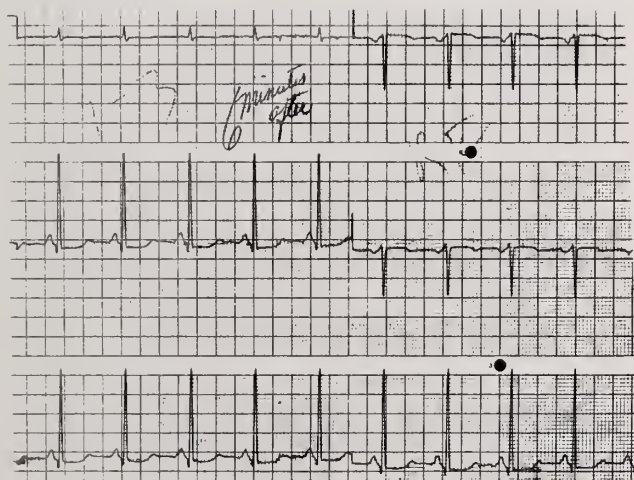


Figure 2a: Exercise electrocardiogram

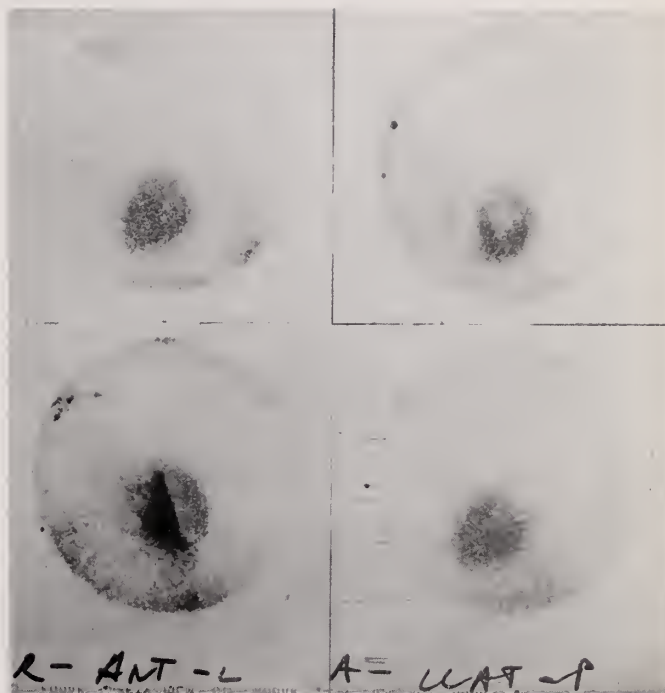


Figure 2b: Exercise ^{201}Tl scan

65° left anterior oblique (top left), 35° left anterior oblique (top right), anterior view (bottom left), left lateral view (bottom right).

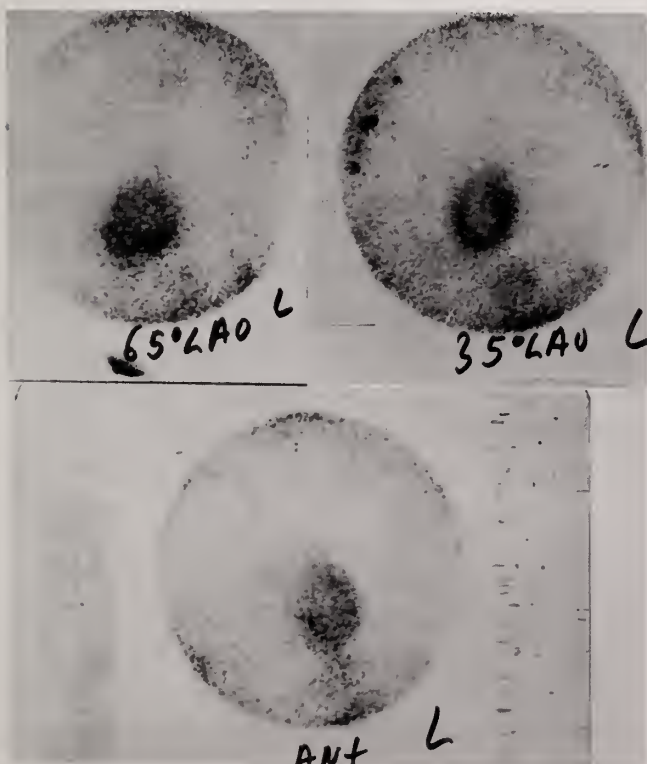


Figure 2c: ^{201}Tl scan delayed images

65° left anterior oblique (top left), 35° left anterior oblique (top right), anterior view (bottom).

heart rate as expected for her age group. The test was stopped due to leg fatigue. Her combined exercise electrocardiogram and myocardial perfusion images are compatible with a) inferior-lateral myocardial ischemia, b) normal response to exercise, c) left ventricular cavity enlargement.

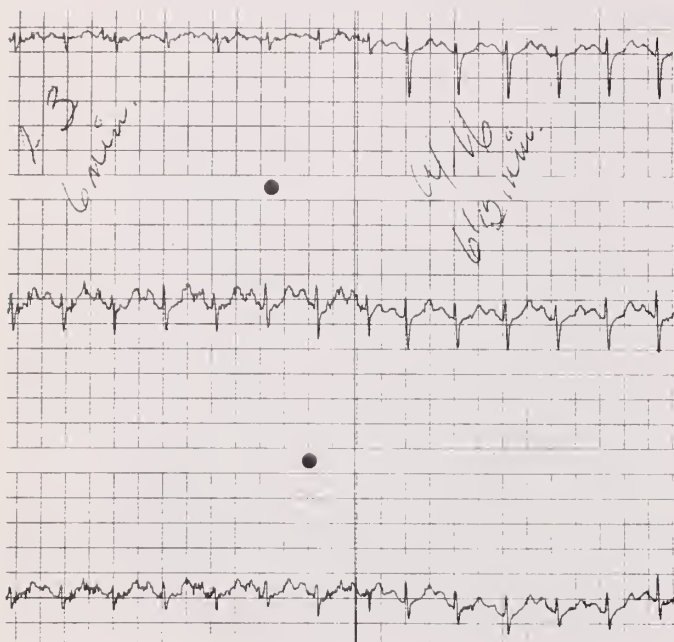
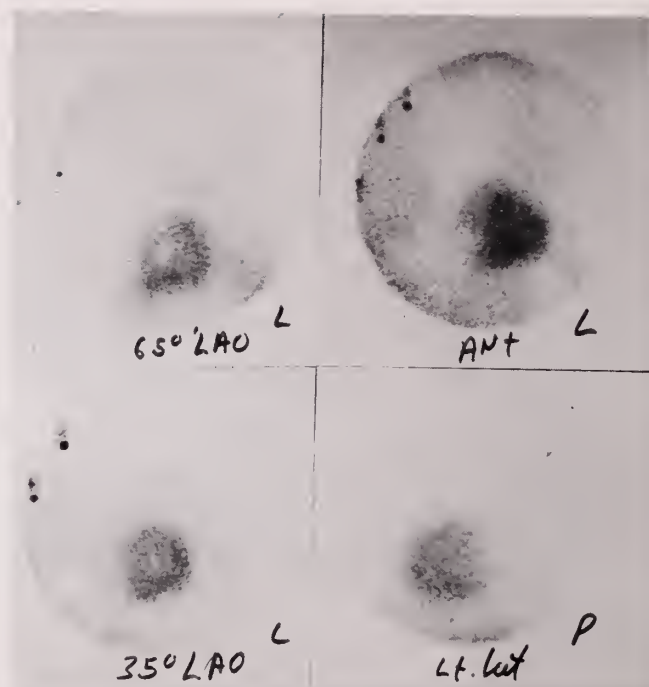


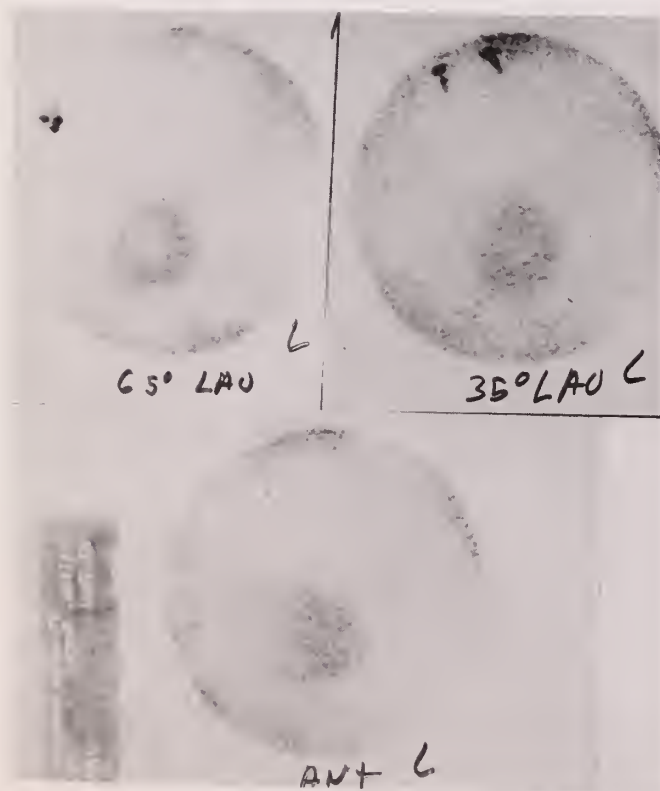
Figure 3a: Exercise electrocardiogram

Figure 3b: Exercise ^{201}Tl scan

65° left anterior oblique (top left), anterior view (top right), 35° left anterior oblique (bottom left), left lateral view (bottom right).

Case 3

This 53-year old female presented with history of retrosternal pain of three months duration. The pain was oppressive, with radiation to the left shoulder, associated with effort, and relieved by rest or sublingual nitroglycerin. Medical history was otherwise non-contributory. Physical examination revealed an obese woman with a blood pressure of 120/80 mm Hg, and pulse 65/min regular. Her thyroid was not palpable and there was no evidence of pulmonary congestion, cardiomegaly, heart murmurs, nor gallops. The ECG at rest showed tendency to low voltage without ST segment abnormalities. A ^{201}Tl myocardial perfusion scan was obtained after the patient exercised for 7 min (100 watts) on a bicycle ergometer. The blood pressure rose to 180/80 and the heart rate was 85 percent of the maximal

Figure 3c: ^{201}Tl scan delayed images

65° left anterior oblique (top left), 35° left anterior oblique (top right), anterior view (bottom).

expected for her age group. The test was stopped due to fatigue. Results of the exercise electrocardiogram and ^{201}Tl scan are compatible with a) normal response to exercise, b) inferior wall ischemia, c) antero-septal and apical segmental ischemia.

Discussion

Case 1

Exercise electrocardiogram failed to show any ST segment displacement and ^{201}Tl myocardial perfusion images disclosed a normal distribution of activity in the left and right ventricular myocardium at the peak of exercise. Delayed images obtained four hours after exercise confirmed the above findings.

Case 2

A horizontal depression of the ST segment in inferior-lateral leads (0.75 mv from the PR segment) was noticed after exercise. The test was interpreted as "equivocal, although highly suggestive of ischemia". However, myocardial perfusion images revealed a normal regional wall perfusion by comparison of the exercise and delayed (4 hrs) films. The relative decrease in activity near the apex and the base of the heart is similar in both sets of films. The former is a normal finding in up to 55 percent of patients due to thinning of apical myocardium and the latter is a normal tapering of activity at the level of the mitral valve plane. Left ventricular cavity was estimated of normal size.

Case 3

Although exercise electrocardiography failed to demonstrate ST segment displacement, exercise ^{201}Tl myocardial images revealed perfusion defects involving the antero-septal and apical segments of the left ventricular wall, abnormalities which were not demonstrated in the delayed films obtained at rest, four hours later. These findings were consistent with coronary artery disease, most likely involving the left anterior descending coronary artery.

These clinical cases illustrate the usefulness of the ^{201}Tl myocardial imaging test in conjunction with the exercise electrocardiogram to provide additional sensitivity and specificity in the diagnosis of chest pain due to myocardial ischemia. This combined examination seems particularly useful not only when prevalence of coronary artery disease is lower (non-cardiac or atypical chest pain as presented in Cases 1 and 2), but also in the case of false negative exercise electrocardiography (Case 3).

Acknowledgment

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AVISO DE INTERES

La Junta Editora, consciente de su responsabilidad de hacer que el "Boletín" cumpla a cabalidad con su cometido de divulgar conocimientos médicos, elevar las normas de educación médica y al propio tiempo de llenar las necesidades de todos los compañeros médicos, ha acordado establecer una nueva Sección que se conocerá como "Sección de Preguntas".

Bajo esta nueva Sección, todos los compañeros tendrán la oportunidad de enviarnos preguntas médicas de casos difíciles o casos clínicos para opinión experta. Estas preguntas, con sus respuestas, serán publicadas en esta nueva Sección.

Las preguntas deberán ser enviadas a:

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Brief Summary

INDICATION: Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.

CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma, Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).

WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle, the patient should therefore be cautioned accordingly. *Drug Dependence:* Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy:* Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children:* Tenuate is not recommended for use in children under 12 years of age.

PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.

ADVERSE REACTIONS: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System:* Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache, rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic:* Urticaria, rash, ecchymosis, erythema. *Endocrine:* Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System:* Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous:* A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.

DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride) One 25 mg. tablet three times daily, one hour before meals, and in the evening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release One 75 mg tablet daily, swallowed whole, in the morning. Tenuate is not recommended for use in children under 12 years of age.

OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976

MERRELL-NATIONAL LABORATORIES Inc.
Cayey, Puerto Rico 00633

Direct Medical Inquiries to

MERRELL-NATIONAL LABORATORIES
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*Studies have shown that obesity is associated with an increased incidence of hypertension, symptomatic heart disease, adult-onset diabetes, and other diseases.

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*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain as shown in animal studies.

¹ Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

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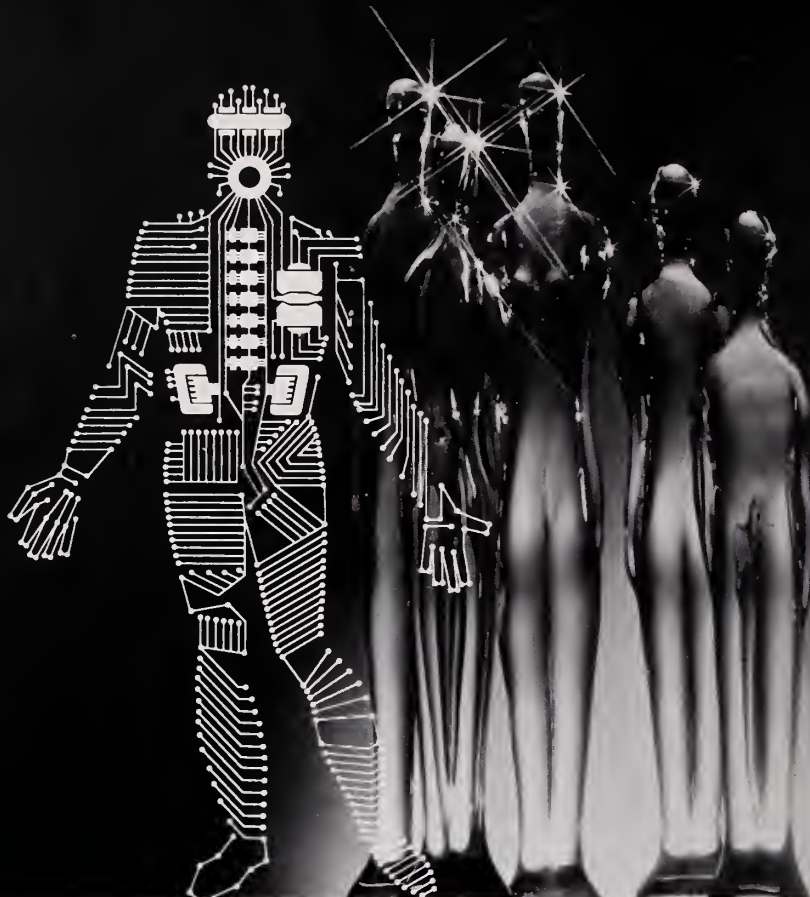
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Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

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Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of

The usual starting dose of Catapres is 0.1 mg at breakfast and 0.1 mg at bedtime. Some patients may benefit from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg

Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chloralhydrate and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000. Also available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

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URINARY TRACT INFECTIONS: DIAGNOSIS AND MANAGEMENT

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R. H. Bermúdez, MD, FACP and C. H. Ramírez Ronda, MD, FACP

Most urinary tract infections occur in women with a frequency that increases with sexual activity and age. It has been estimated that 10 percent to 20 percent of women in the United States will have at least one episode during their lifetime. This situation is quite different for men, in whom infection is rare before 50, and in older men, it usually is associated with prostatic disease or instrumentation of the urinary tract.

The ascending route is the primary pathway by which bacteria enter the urinary tract. The fecal flora provides the major reservoir of infecting microorganisms. The studies of Stamey, however, have demonstrated that vaginal and periurethral carriage of a significant number of pathogenic bacteria is the critical preceding event for the development of bacteriuria in females. In males, the great majority of initial infections can be traced to instrumentation of the urinary tract. The prostate appears to play an important role in recurrent infections in men.

Reinfection and Relapse

The major clinical problem in urinary infection is the great propensity for these infections to recur. Recurrences of bacteriuria are usually divided into two types: reinfection and relapse. *Reinfection* refers to

a recurrence with a new and different organism. It may be the same species but a different serotype, and the fecal flora is the primary source of these new organisms. *Relapse* is a term used for recurrences with the original organisms. To most physicians, this implies that the organism has persisted at some focus within the urinary tract. In females relapse may actually be a reinfection resulting from persistent vaginal carriage of the original organism. Studies suggest that almost all recurrent urinary tract infections in the female are reinfections. On the other hand, recurrence of bacteriuria in males usually represents relapse, but the primary focus of bacterial persistence is the prostate. This is not surprising since most urinary antimicrobials do not penetrate well into prostatic fluid. Relapse also occurs in the presence of urinary calculi. These infections are more common in women and associated with urea-splitting bacteria, specially *Proteus mirabilis*.

Diagnosis

A definitive diagnosis of urinary tract infection rests on the demonstration of significant bacteriuria. Symptoms alone are not sufficient since up to half the women we see with dysuria and frequency will have a sterile urine. Pyuria indicates an inflammation in the urinary tract, but not necessarily infections.

Presence of at least one bacterium per oil-immersion field in midstream, clean-catch gram-stained uncentrifuged urine correlates with $\geq 10^5$ bacteria/ml urine. Gram staining of an uncentrifuged urine specimen is an easy, rapid, and relatively reliable way to detect significant numbers of organisms.

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Suprapubic aspiration of the bladder is extremely reliable method for the diagnosis of urinary infection. Counts as low as 1,000 colonies per ml should be considered indicative of infection as the patient must often force fluids in order to produce the full bladder required for safe needle puncture. This technique has been particularly useful in newborns and infants from whom reliable clean-voided specimens are difficult to obtain.

Bladder catheterization will also provide reliable urine samples for quantitative culture. Catheterization, however, is not recommended for the collection of routine specimens because of the risk of producing bacteriuria in patients presenting with sterile urine. These methods should be reserved for patients who are unable to void spontaneously or to provide a reliable clean voided specimen or for those patients requiring catheterization for urological studies or relief of obstruction.

Localization of the site of urinary tract infection

The ability of the clinician to distinguish between kidney infection and infection restricted to the bladder on the basis of presenting signs and symptoms is quite limited. Better techniques of infection localization are clearly required to fairly evaluate the hypothesis that site of infection affects the clinical course and the response to therapy.

A. Invasive Techniques

The only direct method to localize infection site is bilateral urethral catheterization. The technique involves cystoscopy, is at times technically difficult, and is too invasive for general application. Other method is the washout procedure to localize the site of infection. In this procedure a foley

catheter is introduced into the bladder; the bladder is irrigated with an antibiotic solution (usually neomycin or neomycin and polymyxin); serial samples are collected. Patients with lower tract infection will have sterile urine during the collection period following the washout, while patients with renal infection will have bacteria in all of the post-washout samples. This method is quite satisfactory and most noninvasive techniques of infection localization are now compared to this technique.

B. Noninvasive Techniques

Three types of noninvasive techniques have been employed in an attempt to differentiate between renal and bladder infection: Assay of renal medullary function by measurement of maximal urinary concentrating capacity, measurement of urinary enzymes as an index of tissue invasion and inflammation; and the determination of the immunologic response to the infection. The most promising and presently the most accurate of the indirect techniques for localizing the site of infection, is the demonstration of antibody coating of bacteria in the urine. However, both false positive and false negative results may occur. Vaginal or rectal flora contaminating a urine specimen may give false positive results. Patients with heavy proteinuria may also have false positive results. In males, prostatitis may also be associated with the antibody coating of the infecting bacteria. For reasons as yet unclear, the test appears to be unreliable in children.

Infections in Pregnancy

Urinary tract infections during pregnancy can have serious implications for both the mother and the fetus. Approximately

5 percent of women in the U. S. will have asymptomatic bacteriuria during the first trimester of pregnancy - but this percentage is about the same in non-pregnant females of the same age, however, about one-fourth of these pregnant women will develop a symptomatic infection, primarily pyelonephritis, during the third trimester. The risk of premature delivery also appears to be increased in bacteriuric women, but the incidence of these complications can be significantly reduced by detecting and eliminating bacteriuria in the early stages of pregnancy. Routine screening of all pregnant patients throughout gestation is now a standard obstetrical practice.

Complications

The frequency of progressive renal damage with urinary infections is very low and restricted almost entirely to patients with significant obstructive disease of the urinary tract. It is important, therefore, to identify those patients with infection associated with structural or neurologic abnormalities. These complicated infections occurred more frequently in males and young girls. Urologic studies, including an intravenous pyelogram and cystourethrogram, are indicated in such patients with the first infection. Screening IVP's in teenage and adult women can be reserved for patients with acute pyelonephritis or recurrent infections. Significant obstructive lesions usually necessitate surgical intervention.

Vesico urethral reflux is a frequent finding in young children with bacteriuria. Mild or moderate reflux is rarely associated with progressive renal damage, but when severe, it can lead to caliceal distortion, renal scars, or even atrophic kidneys. Reflux often regresses or even disappears with increasing age and there is growing tendency among urologists not to operate on patients with

mild or moderate reflux, but rather to manage them conservatively to determine if the reflux will regress or disappear with time.

Metastatic infection, secondary to genito-urinary tract sepsis, is usually to skeleton and endocardium. This process has predilection for vertebrae causing osteomyelitis; and endocardium causing infective endocarditis, usually by *S. faecalis* (enterococci).

Papillary necrosis from infection is an acute complication of pyelonephritis usually in the presence of diabetes mellitus, urinary tract obstruction, sickle cell disease or analgesic abuse. The necrotic renal papillae may slough and cause unilateral or bilateral ureteral obstruction.

Perinephric abscess occurs when microorganisms from either the renal parenchyma or blood are deposited in the soft tissues surrounding the kidneys.. It usually occurs secondary to obstruction of an infected kidney or calyx or occasionally secondary to bacteremia. This constitutes a surgical emergency.

Treatment

Antimicrobial therapy is the mainstay of management of urinary tract infections. A large number of antimicrobial agents are available which have the combined characteristics of being active against the common urinary pathogens and also being excreted in high concentration into the urine. The importance of the urinary concentration extends even to infections involving the upper urinary tract because it is the level of drug in the urine that best reflects the concentration present in the medulla.

In terms of bacteriology, *E coli* is the most common urinary pathogen, accounting for 80 percent - 90 percent of all infections. Klebsiella, Enterobacter, Proteus, Pseudomonas, Enterococcus and Staphylococcus are

found less frequently and are more commonly associated with complicated or highly recurrent infections of the urinary tract.

Most initial uncomplicated urinary infections will respond to any of the antimicrobial agent usually recommended. The choice of a specific agent, therefore, should be based on relative cost and toxicity. For these reasons, a short-acting oral sulfonamide such as sulfisoxazole is the agent most commonly recommended. Ampicillin, tetracycline and oral cephalosporins (cephradine, cephalexine and ceclor) are alternative choices, but there is no evidence to indicate that these agents are superior to sulfonamides in the management of either upper or lower urinary tract infection. Ampicillin is the preferred drug for pregnant women near term and in newborn infants because of the potential for sulfonamides to produce kernicterus in newborn.

In vitro antimicrobial sensitivity tests are extremely important in guiding primary therapy in patients with recurrent infections of the urinary tract. The sulfonamides are usually ineffective after the first few courses of therapy. These drugs, as well as ampicillin and tetracyclines, often result in the presence of resistant strains in the fecal flora which then reinfect the urinary tract. It should be remembered that carbenicillin is an important drug in the therapy of systemic *Pseudomonas* infections and that inappropriate use of this agent can lead to development of resistant organisms. Parenteral agents such as the aminoglycosides should be reserved for hospitalized patients with moderate or severe infections of the urinary tract. It is important to remember that 60 percent of the *E. coli* isolated in this hospital are resistant to ampicillin.

No matter which antimicrobial is used, effective therapy should result in a prompt bacteriologic response. Symptomatic improvement alone is a poor indicator of successful

therapy since disappearance of symptoms will occur with minimal suppression of bacteriuria. If it is not free of bacteria at this time, therapy should be switched to another agent. The usual duration of therapy is 10-14 days, and there is some evidence to suggest that a longer course of therapy may be more effective in relapses.

Follow-Up Procedures

Periodic follow-up cultures are important in the successful long-term management of urinary tract infections. They help establish the pattern or recurrence and can provide early clues to the presence of abnormalities of the urinary tract. Studies in young girls and adult women have demonstrated that females stop having frequent recurrences if each episode, whether symptomatic or not, is treated with a short-course of therapy. Approximately 20 percent to 30 percent will go into a long-term remission after each treatment.

The first follow-up culture should be performed one to two weeks after completion of therapy. If negative, additional cultures are obtained at increasing intervals (e.g. once a month for three months, then every three months for one year).

Effective Prophylactic Therapy

In some patients, recurrent episodes are frequent, closely spaced and accompanied by significant morbidity. Prophylactic therapy has proven to be effective, and for women in whom recurrence is related to sexual intercourse, a single oral dose of nitrofurantoin or cephalexin or TMP & SMO after intercourse can reduce the frequency of recurrence. Continuous antimicrobial therapy with trimethoprim-sulfamethoxazole has more general application, but the eradication of bacteriuria

by a course of primary therapy should be demonstrated by culture before embarking on this form of prophylaxis. A half tablet of TMP & SMO at bedtime is highly effective. Continuous therapy is also useful in the management of recurrent infection in males, most studied have used the same dosages as in primary therapy. Periodic monitoring by culture is essential during prophylactic therapy to be sure there is no asymptomatic recurrence.

After six months of prophylactic management, there should be a trial without treatment. The necessary duration of prophylactic therapy will vary from patient to patient.

Catheter Related Infections

The urinary catheter is the leading cause of nosocomial infection and the most common predisposing factor in gram-negative rod bacteremia. Patients requiring long term catheter drainage usually do well even though they are continuously infected. Antimicrobial agents will not eradicate bacteriuria in such patients, and this may lead to colonization with resistant strains. For these reasons, therapy is best reserved for symptomatic episodes of infection.

PRE-QUIZ

I. Match the Best Answer:

1. Bacteriuria
2. Significant Bacteriuria
3. Relapse
4. Re-infection

- a. Numbers of bacteria in voided urine that exceeds the numbers usually due to contamination from the anterior

urethra > 100,000 bacteria/ml.

- b. Numbers of bacteria in voided urine.
- c. Recurrence of bacteriuria with a micro-organism different from the original infecting bacterium.
- d. Recurrence of bacteriuria with the same infecting microorganism which was present before therapy was started.

II. Select the best answer:

1. The most common route by which bacteria can invade and spread within the urinary tract is:

- a. hematogenous
- b. lymphatic
- c. ascending
- d. ascending plus lymphatic
- e. hematogenous plus ascending

2. Which of the following predispose patients to develop urinary tract infections:

- a. obstruction
- b. calculi
- c. vesicourethral reflux
- d. pregnancy
- e. all of the above

3. The most frequent infecting organism in acute pyelonephritis is:

- a. *Proteus mirabilis*
- b. *Escherichia coli*
- c. *Klebsiella-Enterobacter*
- d. *Pseudomonas aeruginosa*
- e. *Staphylococcus epidermidis*

4. False-positive and false negative rates of 20 and 30 percent, respectively make pyuria an unreliable sign of urinary tract infection.

a. true
b. false

5. The presence of at least one bacterium per oil immersion in a midstream, clean catch, gram stained, uncentrifuged urine correlates with $> 10^5$ bacteria/ml of urine.

a. true
b. false

6. M. A. is a 74 y/o male resident of a nursing home who is brought to the emergency room by home personnel at 11:00 p.m. His history includes a cerebrovascular accident several years ago that left him partially paralyzed. Since that event he has had an indwelling urethral catheter. His admitting physical examination reveals a temperature of 102° rectally, regular pulse of 92 beats per minute, and blood pressure of 60/40 mm Hg. His skin is cool and clammy, and his urine output is observed to be less than 20 ml/hr. He is somewhat confused, but the rest of his neurological examination is essential as was described after his CVA. A presumptive diagnosis of UTI with possible sepsis and septic shock is made.

a. Which of the following is a reasonable initial strategy?

1. Admit the patient and observe until the neurologist can see him in the morning.
2. Immediately administer aspirin or acetaminophen to reduce the patient's fever.
3. Immediately start broad-spectrum, antibiotic coverage with a regimen including penicillin G and tetracycline HCl.
4. After gathering proper culture materials and searching the patient's record for recent infection data, start the patient on fluids resuscitation and ampicillin + aminoglycoside.

b. What organism listed is the most likely to cause his infection?

1. *Mycoplasma pneumoniae*
2. *E. coli*
3. *Candida albicans*
4. *S. aureus*

c. Which of the following is important information prior to starting aminoglycoside therapy in this case?

1. Recent and current renal function status
2. Sensitivity reports of recent UTI pathogens
3. Any antibiotic therapy given prior to presenta-

tion at the hospital

4. All of the above

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(Contestaciones en página 425)

ABSTRACTOS DE LITERATURA MEDICA

BISMUTH SUBSALICYLATE THERAPY OF VIRAL GASTROENTERITIS

Steinhoff MC, Douglas RG, Greenberg HB, and Callahan DR - Gastroenterology 75: 1495-1499, 1980.

En este artículo se reporta la eficacia terapéutica de subsalicilato de bismuto (SB) en gastroenteritis viral. Se produjo gastroenteritis en voluntarios dándoles oralmente un inóculo del virus Norwalk. Los que desarrollaron síntomas de gastroenteritis (57 por ciento de 59 voluntarios) se randomizaron a recibir a doble ciegos SB (30 ml. cada media hora por ocho dosis de una preparación muy similar a Pepto-Bismol) o placebo. Se encontró una reducción significativa en la severidad y la duración de dolores abdominales y en la duración media del conjunto de los síntomas gastrointestinales en los que recibieron SB. La mediana de duración de enfermedad (la combinación de síntomas gastrointestinales como diarrea, y síntomas no intestinales como mialgias) fue de veinte horas en los tratados con la preparación de bismuto y de veintisiete horas en el grupo placebo. Los autores no estudiaron el mecanismo de acción de SB en este artículo, pero sugieren que el salicilato en la preparación puede haber afectado el metabolismo de prostaglandinas y de esa forma influenciado procesos de secreción e inflamación.

(Sometido por Angel Olazábal, MD)

AND IN THOSE WITH HAY FEVER AND ASTHMA

E. Chandler Deal, Jr, E. R. McFadden, Jr., et al

La importancia de este estudio lo explica la imperativa necesidad que tenemos todos los clínicos que manejamos y evaluamos pacientes con Asma, de tener una prueba objetiva, simple, sensitiva y no invasiva para diagnosticar esta enfermedad cuando se presenta insidiosamente con síntomas solo de tos o disnea. Al presente solo tenemos pruebas de bronco provocación usando la histamina o la metacolina en dosis diluidas pero incrementadas gradualmente y aplicadas por medio de inhalación.

En el estudio presente los autores describen un método en el cual ellos someten a los pacientes a inhalar aire frío generado externamente por un sistema de intercambio de calor. Los investigadores demostraron que aire inspirado a temperaturas de -10 a -20° C logró lo siguiente:

(1) servir de estímulo potente de broncoconstricción en pacientes no seleccionados asmáticos, (2) no tuvo efecto en función pulmonar en sujetos normales, (3) indujo alteraciones en mecánica pulmonar en sujetos con alergia nasal y con historial de sibilancias en el pecho ocasionalmente.

(Sometido por Iván León, MD)

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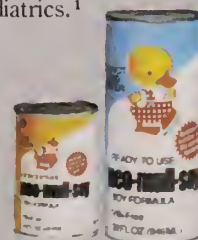
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1. Committee on Nutrition: Commentary on breast feeding and infant formulas, including proposed standards for formulas. *Ped* 52:278-285, 1976.

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Warnings: Usage in Pregnancy—Use in women of childbearing potential only when potential benefits outweigh possible risks

Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped.

Adverse Reactions: Occasionally, drowsiness, dizziness, light-headedness, malaise, overstimulation or gastrointestinal disturbances may be noted, rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, chlorzoxazone may possibly have been associated with gastrointestinal bleeding. While **PARAFLEX**[®] (chlorzoxazone) tablets and other chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately twenty-seven patients, it was not possible to state that the dysfunction was or was not drug induced.

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For information on symptoms/treatment of overdosage, see full prescribing information.

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References: 1. Wallenstein SL, Houde RW. *Fed Proc* 13 414, 1954. 2. Batterman RC, Grossman AJ. *Fed Proc* 14 316, 1955. 3. Vickers FN. *Gastrointest Endosc* 14 94, 1967. 4. Fein FT. *Ann Allergy* 29 598, 1971. 5. Mielke CH, et al. *JAMA* 235 613, 1976. 6. Vernon WG. *Curr Ther Res* 14 801, 1972. 7. Miller AR. *Curr Ther Res* 19 444, 1976. 8. Walker JM. *Curr Ther Res* 15 249, 1973.

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Even among patients with DBP in the low 90s, systematic therapy significantly reduced mortality:

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Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and

related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) in bottles of 100, 1000 and 5000; 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:

1. Five-year Findings of the Hypertension Detection and Follow-up Program: 1. Reduction in Mortality of Persons With High Blood Pressure, Including Mild Hypertension. JAMA 242: 2562, Dec. 7, 1979. 2. Payne, G.H. Presentation of HDFP findings (Nov. 27, 1979), data on file. USV Laboratories

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE FOLLOWING IDIOPATHIC PULMONARY FIBROSIS

McCarthy, D.S., Ostrow, D. N. et al, chest. 77: 4, April, 1980).

Ultimamente se ha hablado mucho de la presencia de enfermedad obstructiva de las vías respiratorias de diámetro menor de 2 mm en enfermedades tales como: sarcoidosis y escleroderma. Este es el 1er. reporte en la literatura americana de dos señoras con fibrosis pulmonar idiopática bien documentada (función pulmonar y biopsia pulmonar) cuyo patrón de disfunción cambió de puramente restrictivo a uno puramente obstructivo en menos de un año.

(Sometido por Iván León, MD)

THE OUTCOME OF PROLONGED COMA IN CHILDHOOD

L. Margoles, MD, and B. A. Shaywitz, MD - Pediatrics: 65: 477, 1980.

The outcome of prolonged coma of non traumatic origin in 16 children is viewed by the authors. Analysis of their clinical courses and neurologic sequelae was made. Identification of factors which may aid in determining prognosis for recovery with a meaningful quality of life was attempted.

The children were evaluated by physical and neurological examination and school reports one to five years after coma.

Six children are normal, six have minor handicaps and four have sustained major sequelae (severe retardation, uncontrolled seizures and blindness).

Anoxia as an etiology of coma and the need for assisted ventilation were significant indicators of a less than normal outcome.

Children in deep coma for greater than two weeks duration tend to be more likely to have neurologic sequelae than those children in coma for shorter

duration.

Prolonged elevated intracranial pressure suggest a less than normal recovery. Also the need for assisted ventilation was a significant predictor for less than normal recovery.

In view of the improving technical capability to care for these children clearly defined and uniform criteria are needed both to assess children during coma and to evaluate them upon recovery.

CHRONIC OTITIS MEDIA IN CHILDREN

Itzhak Brook, MD, MS, Am. J. Dis. Child 134: 564-566, 1980.

Chronic otitis media in children can be insidious, persistent and very often destructive with sometimes irreversible sequelae, such as hearing deficit and subsequent learning disabilities. Bacterial flora of chronic otitis media was studied systematically in pediatric patients with the use of anaerobic techniques.

Aspiration of the exudate through the open perforation was performed in 68 children with chronic otitis media. Aerobes only were isolated from 33 patients (48.5 percent), nine (13.2 percent) had only anaerobes and 26 (38 percent) had a culture which grew both aerobes and anaerobes. Aerobes commonly recovered were *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Proteus* sp., *Klebsiella pneumonia* and *Haemophilus influenza*. Anaerobes commonly isolated were anaerobic Gram positive cocci, *Bacteroides* sp. and *Clostridium* sp.

These findings demonstrate that the bacterial flora of chronic otitis media shows both anaerobes and aerobes that are pathogens of the upper and lower respiratory tract.

Cultures collected from external ear canals prior to sterilization may be misleading. Reliable information can be obtained from the ear exudates when collected through the open perforation in the tympanic membrane.

LEARNING DIFFICULTIES IN CHILDREN OF NORMAL INTELLIGENCE BORN TO ALCOHOLIC MOTHERS

S. E. Shaywitz, MD, D. J. Cohen, MD and B. A. Shaywitz, MD - *J. of Ped.* 96: 978, 1980.

A characteristic cluster of features constitutes the symptom complex termed the fetal alcohol syndrome core components of this syndrome are:

1. Pre and post natal growth deficiency.
2. Dysmorphogenesis manifest primarily as short palpebral fissure, hypoplastic philtrum, thinned upper vermilion and mid facial hypoplasia.
3. Central nervous system dysfunction presenting as mental retardation.

Fifteen children referred to the Learning Disorder Units of the Yale-New Haven Hospital had a history of maternal heavy drinking during pregnancy. The 11 boys and 4 girls ranged in age from 6 1/2 to 18 1/2 years. All growth measurements were affected, 60 percent had head circumference and height less than 10 percentile, 75 percent had weight less than 25 percentile. All the children had the dysmorphic features of the fetal alcohol syndrome.

All had intelligence in the average range (IQ 82 to 113) yet all shared problems of activity and attention regulation.

Alcohol exposure in utero may be an important, preventable determinant of attention deficit syndrome in childhood.

INCIDENCE OF CHOLELITHIASIS IN SICKLE CELL ANEMIA USING THE ULTRASONIC GRAY SCALE TECHNIQUE

S. Sarnack, MBBS, T. Slovis, MD, DP Corbett, MD, A. Emami, MD and C. Whitten, MD - *J. Ped.* 96: 1005, 1980.

Cholelithiasis is known to be commonly associated with Sickle Cell Anemia (hemoglobin SS). Prevalences rates have varied from 10 to 70 percent depending on age and diagnostic criteria.

Gray scale ultrasound examination was performed in 226 patients with sickle cell anemia from 2 to 18 years of age.

Seventy three (27 percent) demonstrated the presence of gall stone, 14 additional patients had "sludge". The incidence of gallstone increased significantly in adolescence.

Ultrasound examination of the gallbladder is a simple, non invasive technique for evaluating the biliary system which is devoid of radiation exposure, rapid and reproducible.

Long term clinical and ultrasound follow up should establish reasonable criteria for cholecystectomy on individuals with sickle cell anemia.

C U R S O S

EMERGENCIES IN INTERNAL MEDICINE - November 2-7, 1980. Sponsored by the University of Miami School of Medicine, Department of Medicine, Division of General Medicine. Sheraton of Bal Harbour, Miami Beach, Florida. A.M.A. Category 1 credit. Information: Division of Continuing Medical Education 023-3, P. O. Box 016960, Miami, Florida 33101. Tele. (305) 547-6716. (SELECTED WORKSHOPS WILL BE OFFERED IN SPANISH).

ADVANCED CARDIAC LIFE SUPPORT/NASSAU CRUISE - November 7-10, 1980. Sponsored by the University of Miami School of Medicine, Department of Medicine, Division of General Medicine. A.M.A. Category 1 credit. Information: Division of Continuing Medical Education D23-3, P. O. Box 016960, Miami, Florida 33101. Tele. (305) 547-6716.

NOTICIAS

AMA RADIO HEALTH & SAFETY TIPS

HICCUPS

When you get a sudden attack of hiccups, it's usually a source of amusement for those around you. But it's not very funny when you're the one hiccupping and trying to breathe normally.

Everyone has his or her favorite home remedy for curing a case of the hiccups, says the American Medical Association. And the reason they always seem to work is that hiccups normally last only a few minutes. They would have stopped anyway, whether you were breathing into a paper bag or being scared silly by a well-meaning friend.

Hiccups are caused by a muscle spasm in the chest, causing you to breathe quickly. Your tongue involuntarily snaps shut across your throat, which makes the recurring sound of "hic."

Many irritants can trigger an attack of hiccups. Eating and drinking too fast; gulping liquids that are too hot or cold; too much smoking; or fatigue. Hiccups should last only a short time. If they continue for more than an hour, it may indicate a more serious condition and medical help should be sought.

IT MUST BE SOMETHING I ATE

Next time you get an upset stomach, don't just dismiss it as "a touch of the flu." Intestinal upsets have many causes, says the American Medical Association. Those same flu-like symptoms—such as nausea, stomach cramps or diarrhea—could be caused by food poisoning.

One common cause of food poisoning is Salmonella. Although food contamination with Salmonella occurs rather frequently, cooking usually kills the Salmonella. Careless food handling is responsible

for the illness of more than one million Americans affected by Salmonella each year.

Botulism is another form of food poisoning we hear a lot about, although it is somewhat rare and is almost always traceable to home canned foods. If you are canning your home-grown vegetables or fruits this year, be sure you have reliable instructions, such as those available from the U. S. Department of Agriculture.

Proper handling of foods, through every step of preparation and storage, is necessary to guard against possible food poisoning. Many meat, poultry and egg dishes can become hazardous if they are allowed to stand too long at room temperature.

The best kitchen philosophy you can live by is, "when in doubt, throw it out."

AMA NEWS

LIVER TRANSPLANT PROGRAM UNDERGOES REEVALUATION

CHICAGO — The Colorado surgical team that pioneered in liver transplantation beginning in 1963 now reports a setback in the program that brought it to almost a halt for a time for reevaluation.

Thomas E. Starzl, MD, of the University of Colorado Health Sciences Center, Denver, reports that of the last 23 cases of liver transplantation, only six individuals survived for as long as one year.

Prior to that time the survival rate had been slowly climbing and had reached 50 per cent in one previous group of 30 patients, Dr. Starzl says.

In studying the poor survival rate of the latest 23 cases, the surgeons determined that a number of factors were involved. Faulty case selection, technical complications, the use of damaged organs, and complications of suppressing the body's automatic factor of

rejecting foreign organs were the main causes of death, Dr. Starzl reports.

A major problem facing the surgical team in liver transplantation is that all of the patients are virtually terminally ill before they are considered for the procedure.

The report appears in the July issue of an American Medical Association specialty journal, *Archives of Surgery*.

The Colorado group previously had reported on 141 cases of liver transplantation, with continued slow improvement in the one-year survival rate.

Mortality in the new group of 23 patients was early. Within one month, eight died, and between 30 and 90 days there were six more deaths. Three more patients died after 4, 6 1/2 and almost 12 months. A final patient died 386 days after transplantation. Five remained alive from 390 to 612 days and were well at the time of preparing the report last winter.

Three of the recipients were so severely ill that, in retrospect, the attempt at transplantation was futile, Dr. Starzl says. Three others received donor livers that never functioned. It remains difficult to determine in advance whether the donor liver is viable. Various other extreme medical problems caused failures of the procedure.

There is no "artificial liver" to prepare patients for the operation or to tide them over if initial graft function is poor. In heart and kidney transplants, machines are available to fulfill the organ's functions before and during surgery.

As the liver program reopens at the Colorado center, the surgeons are applying the knowledge gained in the reevaluation of the 23 cases in the hope of improving the success ratio in the future.

MANY CHEST X-RAYS OF CHILDREN NOT NEEDED

CHICAGO - Routine chest X-rays are not needed in children hospitalized for nonemergency surgery, says a report in the Aug. 8 Journal of the American Medical Association.

It has been common practice in hospitals

throughout the United States to take routine preoperative chest X-rays in all cases of elective surgery in children, Peter B. Farnsworth, MD, Westchester County Medical Center, Valhalla, N. Y., reports.

The rising costs of hospital care and an increased awareness of the dangers of radiation have caused much concern in the medical community, Dr. Farnsworth says. Radiation injuries are more notable in growing tissues and may have more hazardous effects on infants than adults, he declares.

Dr. Farnsworth reviewed 350 cases of elective surgery in children at the medical center. Medical charts and X-ray records were studied. Surgery was never cancelled and the preoperative diagnosis was never changed because of findings on the routine X-ray, he says.

"Our study emphasizes that chest roentgenograms should be obtained only when clinically indicated (in cases of chest health problems)," he concludes.

"We strongly believe that elective surgery in the pediatric age group does not constitute an indication for routine preoperative chest roentgenograms."

ANNUAL CHEST X-RAY URGE IN LUNG CANCER SCREENING

CHICAGO - The effort to economize on cost of routine screening of older men for possible lung cancer has gone too far, says a communication in the Aug. 8 Journal of the American Medical Association.

Mayo Clinic experts in lung cancer announce in an editorial that they are rejecting the recent recommendation of the American Cancer Society that annual chest X-rays be omitted in programs of screening men for lung cancer who have no apparent symptoms.

The ACS recommendation was based, in part, on Mayo Clinic findings, but the doctors say the findings are merely preliminary results and should not be used to make radical changes in the examining procedures.

MDs Robert S. Fontana and David R. Sander-son declare:

"In its efforts to help reduce the cost of medical care, the Cancer Society has apparently failed to

recognize that its recommendations are respected and accepted by practicing physicians, who look to the Society for guidance in patient management.

"The person who requests a cancer checkup is not primarily concerned with cost-benefit analysis, as important as this may be. The person is primarily concerned about cancer and expects the physician to perform those procedures that might detect cancer while it is still curable. For lung cancer, there are only two such procedures, chest roentgenography (X-ray) and sputum cytology (lab study of spittle).

"The American Cancer Society now recommends that neither procedure be performed in asymptomatic (without symptom) persons, even those in the high-risk group (former heavy smokers). We believe that this is a mistake and a disservice to conscientious physicians and their trusting patients, and we urge the Society to reconsider its recommendation."

The Mayo Clinic will continue to recommend annual chest X-rays and lab tests of spittle for men older than age 45 years who have been heavy cigarette smokers, Drs. Fontana and Sanderson declare.

"We believe it is in the best interest of these patients, among whom the prevalence of unsuspected lung cancer approaches 1 per cent. For this group, the risk from an annual chest X-ray is negligible and, we believe, acceptable."

NEWS FROM U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL CANCER INSTITUTE BEGINS LAETRILE TESTS WITH PATIENTS

The first clinical trial of the possible effectiveness of Laetrile (amygdalin) in the treatment of cancer will begin July 1, HHS' National Cancer Institute announced today.

The NCI clinical trial will be carried out simultaneously at four cancer research centers, under the direction of the NCI Investigational Drug Branch of the Cancer Therapy Evaluation Program.

In the course of the study, about 200 cancer patients for whom no other treatment has been effective

will be given Laetrile together with a special diet and supplemental vitamins. The study could take up to two years to complete.

Laetrile, as the chemical amygdalin has come to be known, is a naturally occurring plant product containing glucose, a common sugar. The amygdalin molecule can release hydrogen cyanide, a common poison, when the molecule breaks down in the body. Laetrile is found in the kernels of bitter almonds, apricots, peaches, and plums.

The clinical trial with Laetrile will follow the same testing approach used with other compounds being tested by NCI for effectiveness in treating cancer. Criteria for selecting patients for the Laetrile study are similar to the criteria used for all initial studies of effectiveness of other compounds in the treatment of cancer.

The clinical trial will include patients for whom no established treatment has been demonstrated to be effective. This includes patients who no longer respond to effective drugs, as well as patients for whom no proven treatment exists. All patients must have a measurable cancer—a tumor mass that can be followed through X-ray or other examination for growth or shrinkage.

Before permitting the efficacy testing of the drug, the U. S. Food and Drug Administration last spring required a test of Laetrile for possible toxic effects in a small number of cancer patients. This test was conducted with six patients at the Mayo Clinic to determine whether administration of the drug together with a special diet and supplemental vitamins might be associated with adverse effects. Special care was taken to monitor the patients, particularly with regard to cyanide toxicity.

Five of the six patients experienced no toxic effects that could be directly or indirectly ascribed to Laetrile therapy. The sixth patient showed clinical evidence of toxicity only after eating large quantities of raw almonds, part of the special diet. Raw almonds appear to stimulate the amount and rate of cyanide released if eaten during Laetrile treatment.

The trial will be conducted at the Mayo Clinic in Rochester, Minnesota, by Dr. Charles Moertel; at Memorial Sloan-Kettering Cancer Center in New York City by Dr. Charles Young; at the University of California at Los Angeles Jonsson Cancer Center by Dr.

Gregory Sarna; and at the University of Arizona Health Sciences Center in Tucson by Dr. Stephen Jones. The Mayo Clinic will coordinate the data from all four institutions.

A third clinical study to assess Laetrile's ability to provide relief of symptoms will begin in the near future. This study will measure such clinical effects as pain relief and an increase in the patients' capability to carry out normal daily living functions.

Cancer patients who are interested in taking part in the treatment effectiveness studies should call the National Cancer Information Service toll-free number 800-638-6694 (in Maryland, 800-492-6600; in Alaska and Hawaii, 800-638-6070). Patients who may be eligible will be referred to one of the participating institutions.

II CONGRESO LATINOAMERICANO DE MEDICINA RURAL - 20-25 OCTUBRE 1980

Próximamente se celebrará en Valencia (Es-

paña), el II CONGRESO LATINOAMERICANO DE MEDICINA RURAL, con la participación de importantes personalidades médicas de todos los países de habla hispana.

El Congreso cuenta con el patrocinio de la Organización Mundial de la Salud, así como de los Ministerios de Sanidad, Colegios Médicos y Facultades de Medicina de los 21 países participantes y con la Presidencia de Honor de D. Juan Carlos I, Rey de España.

Se analizará la formación del médico rural, su status así como las consecuencias de la emigración y sus repercusiones en la práctica médica.

Asimismo se estudiará la importancia de la Prevención y Planificación Sanitaria Rural y su relación tanto con la ecología como con los Organismos no estrictamente médicos que colaboran intensamente en el desarrollo de la medicina rural.

JOB OPPORTUNITY FOR AN OBSTETRICIAN/GYNECOLOGIST AT THE NORTHEAST HEALTH CENTER

1. An Obstetrician/Gynecologist is sought to fill a vacancy at the Northeast Health Center to provide Obstetrical/Gynecological care for patient population.
2. This opportunity is for the care of a diffuse population including prepaid, Medicare, Medicaid, and fee for service. The position involves a responsibility at the Rochester General Hospital for teaching and the active Residency program. This opportunity involves an interaction with 3 Internists, and 2 Pediatricians in a multispecialty group practice.
3. The Obstetrician/Gynecologist will interact with Residents from the Associated Hospitals Program of the University of Rochester. The Northeast Health Center in the northeast quadrant of Rochester but serves a patient population from the county wide area. Compensation is competitive and after the initial year is based on productivity.

Licensure in New York State required. If you have questions concerning this please contact Dr. Neil W. Garroway, Telephone No. 716-482-4300.

ANUNCIOS

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- ☐ Minimal interference with many primary medications, such as antacids, anticholinergics, diuretics, cardiac glycosides and antihypertensive agents

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

Use in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and

acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. Oral—Adults: Mild and moderate anxiety and tension, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.)

Supplied: Librium® (chlordiazepoxide HCl) Capsules, 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Libritabs® (chlordiazepoxide) Tablets, 5 mg, 10 mg and 25 mg—bottles of 100 and 500. With respect to clinical activity, capsules and tablets are indistinguishable.

synonymous with relief of anxiety

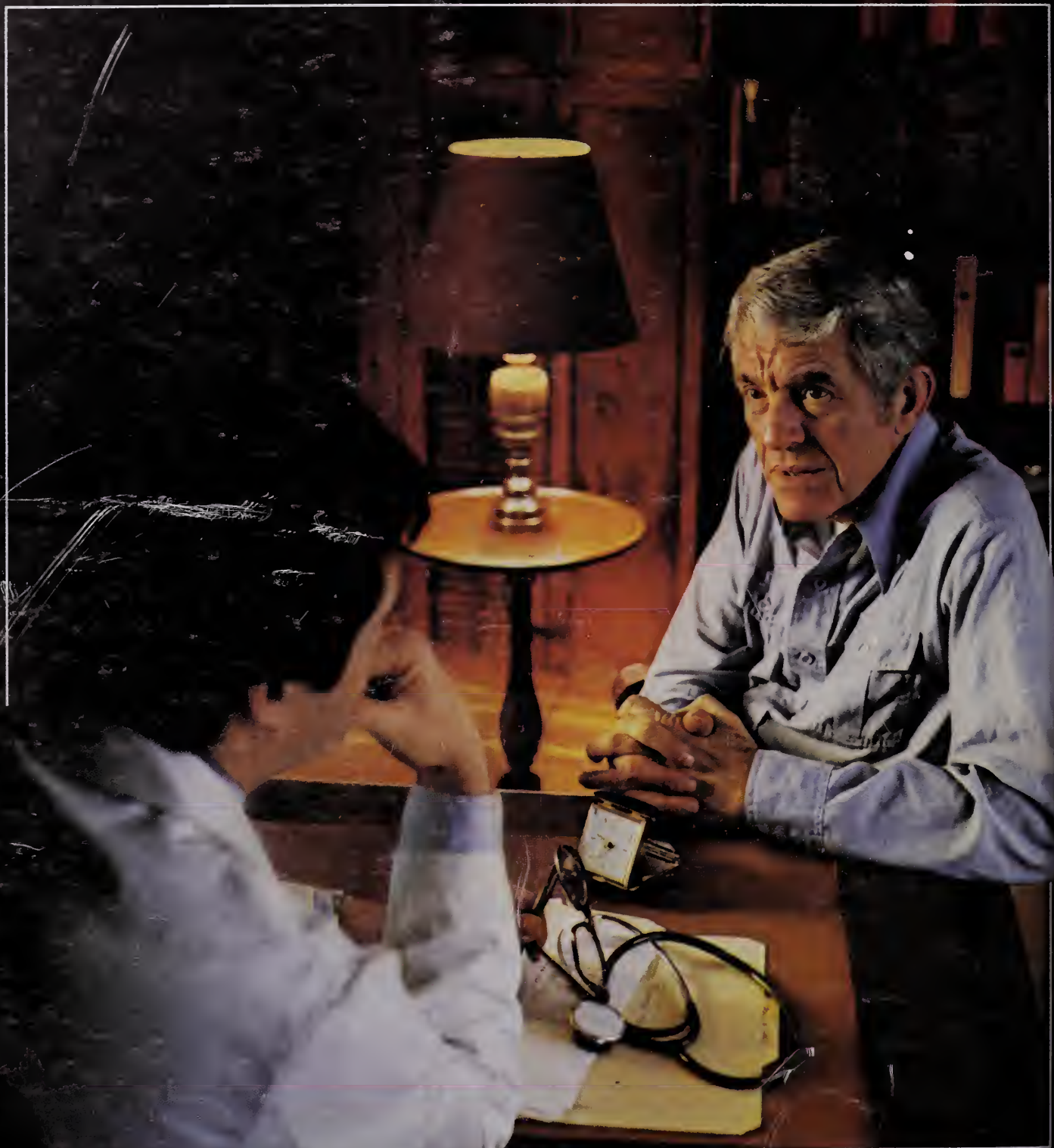
ROCHE

Roche Products Inc.
Manati, Puerto Rico 00701

Please see following page.

Librium®

chlordiazepoxide HCl/Roche
5 mg, 10 mg, 25 mg capsules



synonymous
with relief of anxiety



Please see preceding page for a summary of product information.



BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

CONTENIDO:

INSULINOMA: DIAGNOSIS AND MANAGEMENT

FORO DE MEDICINA NUCLEAR:
SUPRESION DEL TIROIDES POR TRIYODOTIRONINA

TRATAMIENTO AMBULATORIO DEL ASMA BRONQUIAL EN LOS NIÑOS

EDITORIAL: CARDIOLOGIA PEDIATRICA

MEDI-QUIZ (2)

ABSTRACTOS DE LITERATURA MEDICA

CARTA AL EDITOR

TRABAJOS PRESENTADOS EN LA REUNION ANUAL
AMERICAN COLLEGE OF PHYSICIANS – OCTUBRE 1980

BUZON DEL LECTOR

CURSOS – GRAPHICS – NOTICIAS

INDICE PAGINA 455

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half-life

Just one built-in advantage

Ensures smooth therapeutic effect even if a dose is missed The relatively longer half-life of Valium® (diazepam/Roche) has important clinical and pharmacological implications. Steady-state levels generally are reached within 5-7 days with no further accumulation. At this plateau, the patient benefits from the consistent, steady response you expect. Sharp blood level variations, frequently attributed to agents with a short half-life, do not appear with Valium.

Avoids sudden symptom breakthrough

Once steady-state levels are achieved, sudden reemergence of symptoms is unlikely. Diazepam and its active metabolites exhibit overlapping half-lives that are advantageous not only during therapy but especially when pharmacologic support is discontinued.

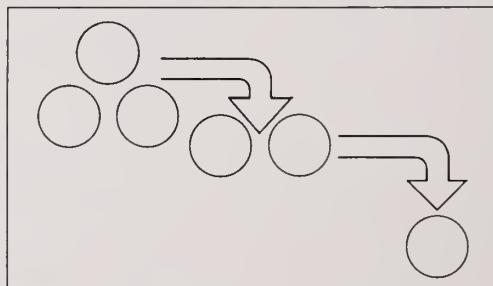
Elimination rates are gradual with Valium and thus provide a compatible adjustment interval for

the patient. In comparison, blood levels of short-acting agents with inactive metabolites decrease more rapidly and are more likely to be associated with withdrawal symptoms if medication is stopped abruptly.* With Valium unwanted effects other than drowsiness or ataxia are rare. Patients should be cautioned about driving and advised to avoid alcohol.

Tapers naturally; complements gradual dosage reduction at discontinuation

When any psychoactive medication is discontinued, it is good medical practice to gradually reduce the dosage. From your own experience you know this is rarely necessary after a short course of Valium therapy, but for patients on extended therapy, gradual reduction of dosage is advisable. This regimen, along with the self-tapering feature of Valium, provides a smooth transition to independent coping.

*Sellers EM: *Drug Metab Rev* 8(1):5-11, 1978



*in the management of
symptoms of anxiety*

Valium®
diazepam/Roche
2-mg, 5-mg, 10-mg scored tablets

*effective therapy through
efficient pharmacodynamics*

Before prescribing, please see summary of product information on next page



Valium[®] diazepam/Roche

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety, symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal, adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, atetosis, stiff-man syndrome, convulsive disorders (not for sole therapy)

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication, abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.

LISTA DE ANUNCIANTES

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Septra

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TIGHT CONTROL OF INFLAMMATION



in rheumatoid arthritis* and osteoarthritis:

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(TOLMETIN SODIUM) DOUBLE STRENGTH
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one capsule *t.i.d.*
for a more convenient
starting dose

Double strength, nonsteroidal capsules offer...

- **Rapid control of inflammation**
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- **Dependable, long-term management of chronic symptoms**

Peak plasma levels are reached within 30 to 60 minutes. A therapeutic response can be expected in a few days to a week. And *Tolectin* tolmetin sodium is well tolerated: the frequency of milder gastrointestinal adverse effects and tinnitus has been shown to be less than with aspirin.

*For patients classified as Functional Class IV (incapacitated with little or no self-care), safety and effectiveness have not yet been established.

Please turn page for brief summary of prescribing information.

SUMMARY OF PRESCRIBING INFORMATION

TOLECTIN® DS (tolmetin sodium) double-strength capsules— for oral administration

Description: *TOLECTIN DS* (tolmetin sodium) capsules contain tolmetin sodium as the dihydrate in an amount equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium.

Contraindications: *Tolmetin* (tolmetin sodium) should not be used in patients who have previously exhibited intolerance to it or patients in whom aspirin and other non-steroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria.

Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported.

If *Tolmetin* must be given to patients with active peptic ulcer, closely supervise the patients for signs of ulcer perforation or severe gastrointestinal bleeding.

Precautions: *General*—Clinical studies of up to two years duration have shown no changes in the eyes attributable to *Tolmetin* (tolmetin sodium) administration; however, because of ocular changes observed clinically with other non-steroidal anti-inflammatory drugs, ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.

There has been no evidence of renal toxicity to date in clinical studies; however, since *Tolmetin* is eliminated primarily by the kidneys, closely monitor patients with impaired renal function; they may require lower doses.

Tolmetin prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when *Tolmetin* is administered.

In patients receiving concomitant *Tolmetin*-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

Tolmetin should be used with caution in patients with compromised cardiac function.

The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g. sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips (e.g. Albustix®, Unstix®, etc.).

Usage in Pregnancy—Since *Tolmetin* has not been studied in pregnant women, the use of *Tolmetin* during pregnancy is not recommended.

Nursing Mothers—Because *Tolmetin* may be secreted in human milk, as a general rule nursing should not be undertaken while a patient is on this drug.

Drug Interactions—Although *Tolmetin* has been found *in vitro* to bind extensively to plasma protein, it does not alter the dosage of warfarin required to maintain a uniform prothrombin time.

In adult diabetic patients under treatment with either sulfonylureas or insulin, there is no change in the clinical effects of either *Tolmetin* or the hypoglycemic agents.

Adverse Reactions: Gastrointestinal System—The most frequent adverse reactions which occurred were gastrointestinal: nausea, 1 in 9 patients; dyspepsia, 1 in 10 patients; abdominal pain, 1 in 15; gastrointestinal distress, 1 in 15; flatulence, 1 in 25; diarrhea, 1 in 25; constipation, 1 in 40; vomiting, 1 in 30; gastritis, 1 in 55; and significant gastrointestinal bleeding without evidence of peptic ulceration, 1 in 240.

The incidence of peptic ulcer in about 3000 patients treated up to two years in clinical studies was about 1 in 50. Thirty-four percent of the ulcer patients had prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs, including corticosteroids, known to produce peptic ulceration.

In clinical trials about 10% of patients dropped out because of adverse reactions, mostly gastrointestinal in nature.

Body as a Whole—headache, about 1 in 10 patients; asthenia and chest pain, less frequently; and, rarely, anaphylactoid reactions.

Cardiovascular—edema, about 1 in 15 patients; hypertension, less frequently.

Central Nervous System/Psychiatric—dizziness or lightheadedness, about 1 in 20 patients; tension or nervousness, 1 in 50 patients; drowsiness, 1 in 60 patients; insomnia and depression, less frequently.

Dermatologic—rash, about 1 in 40 patients; pruritus, 1 in 60 patients; skin irritation, 1 in 55 patients.

Special Senses—tinnitus, about 1 in 65 patients.

Hematologic—Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred. This is similar to that reported with other non-steroidal anti-inflammatory drugs. A few cases of granulocytopenia have been observed.

Caution: Federal law prohibits dispensing without a prescription.

Full directions for use should be read before administering or prescribing.

For information on symptoms and treatment of overdosage, see full prescribing information.

Also available: *TOLECTIN®* (tolmetin sodium) tablets 200 mg. DEPOT STOCKED 500's.
Military 6505-01-030-3241,
VA 6505-01-030-3241 A

972201

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Lung cancer is now an equal opportunity tragedy.

Remember when lung cancer was a man's disease. Because men had been smoking longer than women. But the women's smoking boom that started in the 1930's and 40's—is paying most cruel dividends today. Yet most people still think lung cancer is a man's disease. Tell your female patients the true story. That lung cancer is now an equal opportunity tragedy. That's what "you've come a long way, baby" is all about.

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Office on Smoking and Health
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ASOCIACION MEDICA DE PUERTO RICO

(USPS-060000)

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Fundado en 1903

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ASOCIACION MEDICA DE PUERTORICO

VOLUMEN 72

INDICE

SEPTIEMBRE 1980

NUMERO 9

- * **Insulinoma: Diagnosis and Management** 455
Francisco Aguiló, Jr. MD, FACP, Vilma M. Rabell, MD, Myriam Allende, MD and Enrique Vázquez Quintana, MD, FACS

Although insulinoma is one of the most frequent etiological factors sought in the evaluation of adult patients with hypoglycemia, the entity remains an unfrequent and rare cause of this metabolic disturbance. Among 250 patients referred to the Division of Endocrinology at the University District Hospital, the diagnosis of insulinoma was clearly established in only one patient. In this issue Aguiló et al present the clinical metabolic and pathological features of this very interesting patient. In the discussion, which comprises a complete review of the literature, the author emphasizes that in 92 percent of the published cases in the world literature, the presenting symptoms were neuropsychiatric in origin: sluggishness, confusion, asthenia, disturbed vision and coma.

Although there have been other cases diagnosed in Puerto Rico, this is the first documented case published in our journal. This communication should be of great interest to all of our readers.

- * **Foro de Medicina Nuclear: Supresión del Tiroides por Triyodotironina** 466
José de Jesús Herrera, MD

En esta edición, el Dr. Herrera demuestra la utilidad de la supresión del tiroide por triyodotironina en la evaluación de pacientes hipertiroides que han estado en tratamiento por tiempo prolongado. Se presentan dos pacientes con historial de hipertiroidismo tratados por varios años. En ambos pacientes, la captación de iodo radioactivo en 24 horas es normal. Después de una semana de tratamiento con triyodotironina, se demuestra que un paciente tiene glándula eutiroides autónoma (captación de iodo y centelleo del tiroides permanecen iguales), mientras que el otro paciente tiene una glándula tiroides normal, no autónoma (la captación de iodo disminuye, el centelleo del tiroides demuestra una disminución de la actividad del tiroides en relación con el fondo y glándulas salivares).

- * **Tratamiento Ambulatorio del Asma Bronquial en los Niños** 469
José E. Sifontes, MD, Pedro M. Mayol, MD, Wilfredo Vélez, MD, Efraín Alicea, MD, Frank Rodríguez Martínez, MD y Juan J. Santana, MD

Uno de los problemas más comunes en Puerto Rico; asma bronquial, es presentado y discutido extensamente por Sifontes et al, en esta edición del Boletín. Observaciones hechas por los autores, indican que al presente el tratamiento ambulatorio de la mayoría de los niños afectados es insatisfactorio. Los autores enfatizan que en muchos de los casos, el asma bronquial no es de origen alérgico. Otros factores importantes parecen ser la

contaminación del aire, las infecciones respiratorias virales, cambios barométricos y de temperatura, ejercicios y posiblemente factores emocionales.

La teofilina y los broncodilatadores agonistas beta son los fundamentos y base de la farmacoterapia de esta condición médica. Les recomiendo a todos, internistas, pediatras, y médicos de familia, la lectura cuidadosa de este artículo.

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AVISO DE INTERES

La Junta Editora, consciente de su responsabilidad de hacer que el "Boletín" cumpla a cabalidad con su cometido de divulgar conocimientos médicos, elevar las normas de educación médica y al propio tiempo de llenar las necesidades de todos los compañeros médicos, ha acordado establecer una nueva Sección que se conocerá como "Sección de Preguntas".

Bajo esta nueva Sección, todos los compañeros tendrán la oportunidad de enviarnos preguntas médicas de casos difíciles o casos clínicos para opinión experta. Estas preguntas, con sus respuestas, serán publicadas en esta nueva Sección.

Las preguntas deberán ser enviadas a:

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Sección de Preguntas
Apartado 9387
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Esperamos sus preguntas.

Juan M. Aranda, MD
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Tenuate® (C)

(diethylpropion hydrochloride NF)

Tenuate Dospan®

(diethylpropion hydrochloride NF) controlled-release

AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

INDICATION: Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.

CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma, agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).

WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle, the patient should therefore be cautioned accordingly. *Drug Dependence:* Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy:* Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children:* Tenuate is not recommended for use in children under 12 years of age.

PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.

ADVERSE REACTIONS: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System:* Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache, rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic:* Urticaria, rash, ecchymosis, erythema. *Endocrine:* Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System:* Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous:* A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.

DOSE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride) One 25 mg tablet three times daily one hour before meals, and in mid evening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release One 75 mg tablet daily, swallowed whole, in mid morning. Tenuate is not recommended for use in children under 12 years of age.

OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976

MERRELL-NATIONAL LABORATORIES Inc
Cayey, Puerto Rico 00633

Direct Medical Inquiries to
MERRELL-NATIONAL LABORATORIES
Division of Richardson-Merrell Inc
Cincinnati, Ohio 45215, U.S.A.

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References: 1. Citations available on request from Medical Research Department, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon [Dillon], R.H., and Leyland, H.M. A comprehensive review of diethylpropion hydrochloride. In: Central Mechanisms of Anorectic Drugs. S. Garattini and R. Samanin, Ed. New York, Raven Press, 1978, pp. 391-404.

Merrell

**Overweight may not always be simple...
complications can develop*.
Complicated or not...**

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A useful short-term adjunct in an indicated weight loss program.

Overweight patients in certain diagnostic categories often require strict appetite control and a successful program of weight reduction may tend to diminish the incidence or severity of the complications in some patients. Diethylpropion hydrochloride has been reported useful in such patients and while it is not suggested that Tenuate itself in any way reduces the complications of overweight, it may have a useful place as a short-term adjunct in a prescribed dietary regimen. **Tenuate should not be administered to patients with severe hypertension; see additional Warnings and Precautions on the opposite page.**

In uncomplicated overweight.

Many patients, on the other hand, present with excess fat but no disease. While this condition is often termed uncomplicated obesity, complications of both a social and a psychologic nature may be distressingly real for the patients. In these cases, a short-term regimen of Tenuate can help reinforce your dietary counsel during the important early weeks of an indicated weight loss program.

Clinical effectiveness.

The anorectic effectiveness of diethylpropion hydrochloride is well documented. No less than 16 separate double-blind, placebo-controlled studies attest to its usefulness in daily practice.¹ And the unique chemistry of Tenuate provides "...anorectic potency with minimal overt central nervous system or cardiovascular stimulation."² Compared with the amphetamines, diethylpropion has minimal potential for abuse.

**Tenuate—it makes sense.
And it's responsible medicine.**

*Studies have shown that obesity is associated with an increased incidence of hypertension, symptomatic heart disease, adult-onset diabetes, and other diseases.

Merrell



For prescribing information see opposite page

In G.I. therapy



Adjunctive
Librax[®]

Each capsule contains
5 mg chlordiazepoxide HCl
and 2.5 mg clidinium Br

antianxiety/antisecretory/antispasmodic
for adjunctive therapy of duodenal ulcer*
and irritable bowel syndrome*

Librax[®]

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma, prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Bromide.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium[®] (chlordiazepoxide HCl/Roche) to known addic-

tion-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug

and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, i.e., dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets

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INSULINOMA: DIAGNOSIS AND MANAGEMENT

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Summary: A 60-year old white female had episodes of dizziness, increased sweating and loss of consciousness which were relieved by food ingestion. She had gained 20 lbs. in the preceding 18 months. For over 8 years she had been treated for psychiatric manifestations. After a diabetes screening she was placed on a weight reduction diet which aggravated her symptoms. Fasting hypoglycemia (22 mg/dL) and hyperinsulinism (up to 1,400 μ U/ml) were documented. At celiac arteriography, a well defined mass was seen in the tail of the pancreas, which proved to be an insulinoma at operation. Post operatively she developed a pseudocyst which resolved without operation. Persistent hyperglycemia (up to 276 mg/dL fasting) and glycosuria were not responsive to sulfonylureas. After almost achieving ideal body weight, she was prescribed 20 units of insulin daily, a treatment which she still follows.

This was the first case of insulinoma

diagnosed and fully work-up preoperatively in Puerto Rico. Such tumors remain a rare cause of hypoglycemia.

Resumen: Se presenta el caso de una señora de 60 años que padecía de mareos, sudoración y pérdida de conocimiento, aliviados por la ingestión de alimentos. Había ganado 20 libras de peso en 18 meses. Se había tratado por más de ocho años por manifestaciones psiquiátricas. Tras una prueba de discernimiento de diabetes fue puesta en una dieta adelgazante que agravó los síntomas. Se documentó una hipoglucemia de 22 mg/dL acompañada de un hiperinsulinismo, el cual llegó hasta niveles de 1,400 μ U/ml. El estudio arteriográfico celíaco demostró una masa bien definida en la cola del páncreas, la cual se confirmó era un insulinoma durante la operación quirúrgica. El curso post-operatorio fue complicado por la formación de un pseudoquistes, el cual resolvió sin intervención. Se instaló una hiperglucemia (de hasta 276 mg/dL) y una glucosuria que no respondieron a un intento terapéutico con sulfonilureas durante 6 meses. Luego de conseguir casi su peso ideal, se comenzó en 20 unidades de insulin diarias, lo cual sigue al presente.

Este ha sido el primer insulinoma que se haya diagnosticado y estudiado pre-operatoriamente en Puerto Rico. Dichos tumores son una causa rara de hipoglucemia.

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Introduction

After a 15-year search, during which we evaluated over 250 patients referred with "hypoglycemia", we discovered our first patient with an insulinoma, that we report herein. It is noteworthy that this patient developed permanent clinically manifest and insulin-dependent diabetes mellitus after tumor resection.

Case Report

A 60-year old white female was referred to us for further evaluation of hypoglycemia and a history of weight gain (20 lbs. in 18 months). A screening test for diabetes in January, 1974 had shown a 2 hr. post prandial blood glucose of 154 mg/dL. A reducing diet made her symptoms worse. Dizzy spells had sometimes been accompanied by increased sweating and loss of consciousness, had occurred at any time of the day and were relieved by food ingestion.

There was history of psychiatric treatment during the preceding 8 years. She had been followed at the Neurology Clinic for headaches, lumbar and cervical pains, for the past 3 years. Her work-up, including an EEG, brain scan and skull films had been negative.

The patient manifested an array of bizarre symptoms, like at times removing her clothes and attempting to go outnaked, and watching boiling milk spilling and do nothing about it. She also became angry and start crying with little provocation. For such symptoms she had been given major tranquilizers.

Her past history was non-contributory. She was Gr VI P VI Ab I (a pair of twins died neonatally), and had a 7 months stillbirth. None of her children had weighed over 8 lbs. There was no family history of diabetes mellitus, or other endocrine disease.

Her review of systems disclosed headaches, chest pains, and dyspnea on exertion. There was also nausea and fatty-food intolerance.

Physical examination revealed an obese elderly female with a pleasant disposition. Her affect and orientation appeared to be normal. She looked pale. Weight: 193 lbs. (87.7 kg); height: 61 inches (1.55 m). B. P.

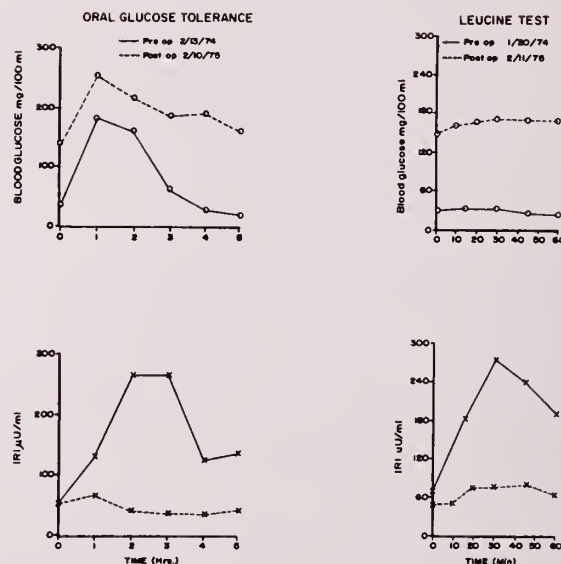


Fig. 1: Oral glucose tolerance and leucine test pre and post operatively.

140/90, P. 82/min, regular. Fundoscopic and neurological exams were negative. The abdomen was globular but there was no hepatosplenomegaly or masses. There was no abdominal tenderness. Axillary and pubic hair were somewhat diminished but probably adequate for age.

Laboratory Data:

Complete blood counts, urinalysis, electrolytes and chemical profile were all normal. A 5-hour oral glucose tolerance test (100 Gm dose) at our laboratory showed the following values (mg/dL): Fasting: 35, 1 hr. 179, 2 hr. 160, 3 hr. 64, 4 hr. 29 and 5 hr. 22. Immunoreactive insulin (IRI) values were: 54, 132, 268, 268, 128 and 138 μ U/ml respectively. Baseline 24 hr. urinary 17-hydroxysteroids were 8 mg, and post Metopirone, 16.2 mg/24 hrs. A 24 hr. 131 I uptake by the thyroid was 7.3 percent and post-TSH, 16.8 percent. Total serum thyroxine was 5.9 μ gm/dL. Radiological examinations of the chest, skull and stomach were all negative. Liver and spleen scan were normal.

BLOOD GLUCOSE AND IMMUNOREACTIVE INSULIN DIURNAL PATTERN IN PATIENT WITH INSULINOMA PRE AND DIAZOXIDE THERAPY

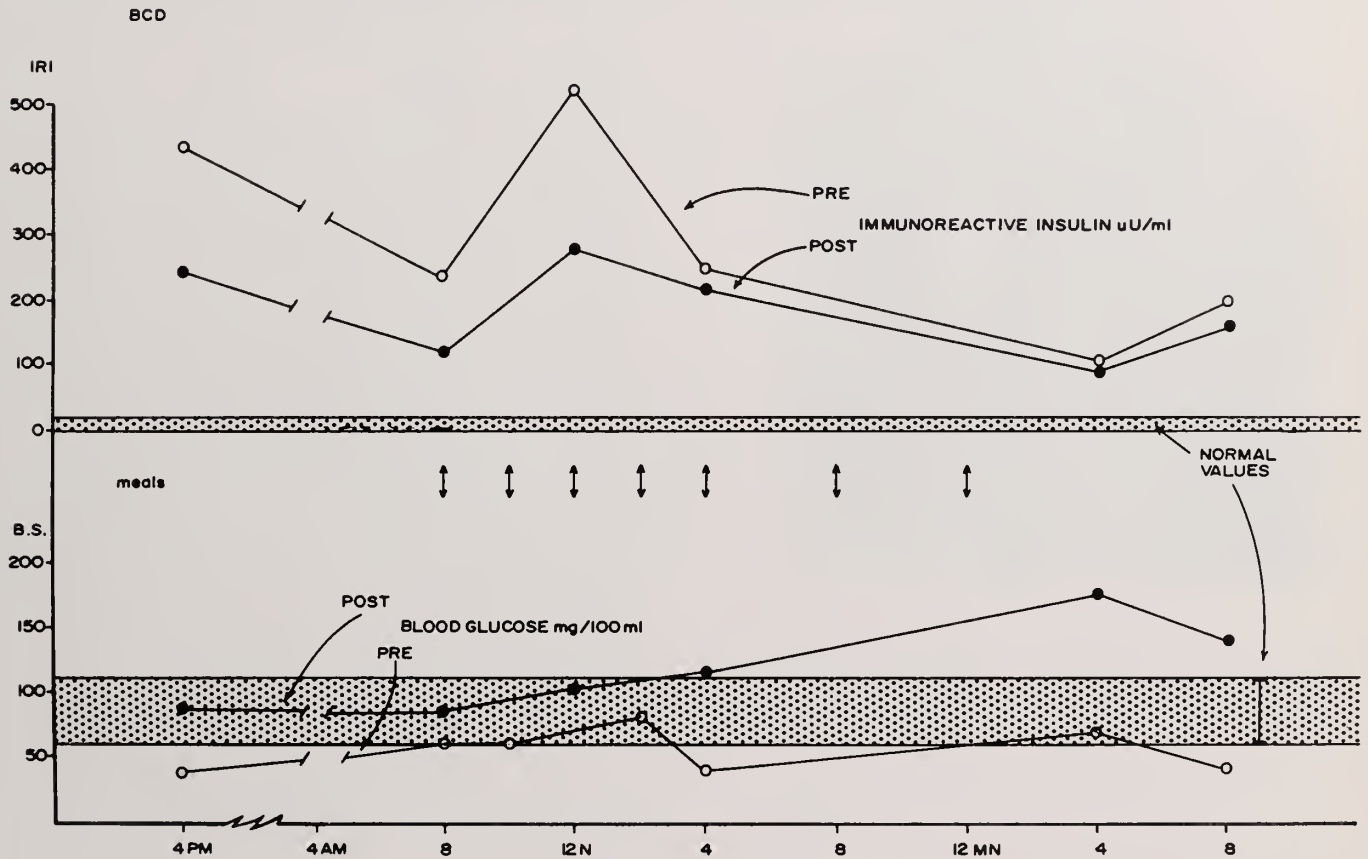


Fig. 2: Blood glucose and immunoreactive insulin diurnal pattern pre and during diazoxide therapy.

Hospital Course and Additional Studies

The patient was placed on a prolonged fast but it failed, as she took some food on her own. She was then moved into a barren room without bedside tables. Twenty hours after a closely supervised fast she developed aberrant conduct, deviation of her eyes to the right and salivation. Intravenous glucagon (1 mg) gave prompt recovery from such symptoms. At that time blood glucose was 16 mg/dL and IRI was 38 μ U/ml. A rapid intravenous GTT gave a k value of 1.5 percent. A leucine test (150 mg/Kg) was done and is depicted in Fig. 1. A modified tolbutamide test (1 Gm I.V.) was performed, primed by a 25 Gm

glucose bolus followed by a sustained 15 percent glucose infusion (Table I). All these tests confirmed hyperinsulinism out of proportion to glucose values. During the OGTT IRI went up 5-fold, from 54 to 268 μ U/ml, at 2 and 3 hrs. In spite of almost no change in blood glucose, leucine caused a 4-fold increase in IRI (from 70 to 280 μ U/ml at 30 min) and I. V. tolbutamide increased IRI almost 3-fold (from 557 to 1,400 μ U/ml).

While at the Clinical Research Center, diazoxide p.o. was started at 400 mg/day. This elevated diurnally-monitored blood glucose so that 48 hours later hypoglycemia was no longer present. IRI values were similarly lower (Fig. 2).



Fig. 3: Celiac arteriography demonstrating the tumor (arrow).

Celiac arteriogram revealed a well-defined area of increased vascularity at the left side of T-12 and L-1, measuring 3 x 2.5 cm (Fig. 3). The patient was then readmitted to the Surgery Department. Her fasting glucose was around 200 mg/dL, while on 200 mg diazoxide daily. Two days prior to surgery diazoxide was discontinued, in order to monitor blood glucose intraoperatively.

At operation, such monitoring was hampered by mal-functioning of the reflectance meter utilized, which prompted administration of 10 percent glucose solution for non-existent hypoglycemia (Fig. 4). In fact, as judged by subsequent auto-analyzer values, such therapy resulted in an elevation of blood glucose from 120 mg/dL to over 200 mg/dL. Concomitantly, IRI increased from 160 to near 900 μ U per ml.

Operative Findings

A 3.5 x 2.5 x 2.5 violaceous-pink nodule was easily found and enucleated from the tail of the pan-

creas. This caused a sharp increase in blood glucose to 400 mg/dL and a precipitous drop of IRI (Fig. 4). No evidence of hepatic or other metastases were found.

Pathological Findings

The tumor was well encapsulated and could be totally removed from surrounding tissues. It weighed 11.22 Gm. It was very firm to palpation and resisted cutting. Light microscopy showed typical features of islet cell tumor, consisting of cords and nests of well-differentiated cells with finely granular cytoplasm, separated by dense, abundant fibrosed stroma, best shown by its blue staining with Masson trichome. There was no evidence of vascular or perineural tumor infiltration. Electron microscopy of the tumor revealed well-differentiated and abundant beta cells with characteristic intracytoplasmic secretory granules, forming a dense central core surrounded by a clear halo (Fig. 5A). The adjacent tissue revealed an abundant number of alpha cells having characteristic dark granules and no clear halo, with a scarcity of beta cells (Fig. 5B).

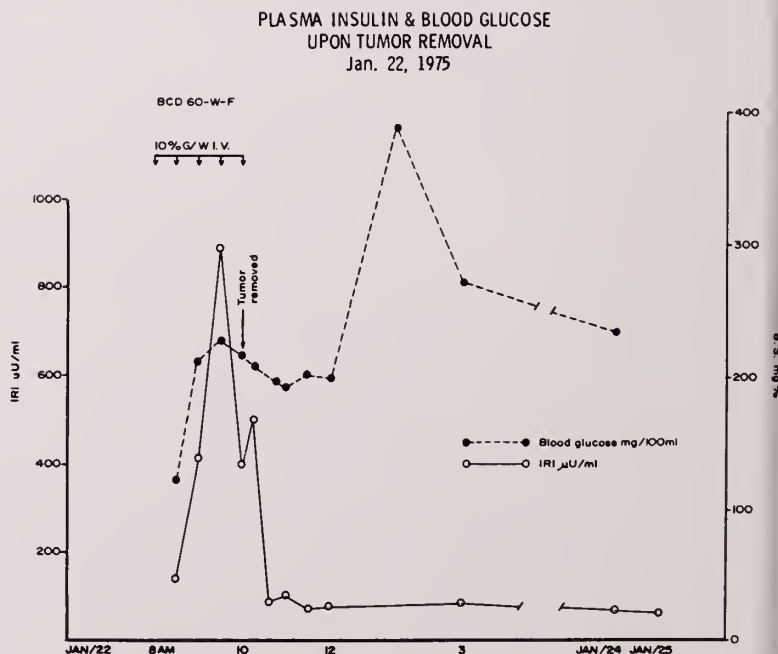


Fig. 4: Intra and post-operative blood glucose and immunoreactive insulin levels (See text).

TABLE I

Intravenous Tolbutamide Test in Insulinoma (Pre and Post Op)

Pre-Op (11/22/74)			Post Op (2/7/75)		
Time (min)	Glucose (mg/dL)	IRI (uU/ml)	Time (min)	Glucose (mg/dL)	IRI (uU/ml)
BL*	285	270	BL	161	18
20 +	189	365	10	163	75
30 +	168	330	20	161	
40 +	154	405	30	158	50
50 +	144	542	45	152	50
60 +	137	557	60	147	70
(Tolbutamide 1 GM I.V.)					
10	114	1400	120	125	25
20	93	1300	150	114	
30	71	1130	180	103	30
45	45	1130			
60	30	1300			
90	15	850			

* - BL - baseline, post IV bolus of 25 Gm glucose as 50 percent G/W

+ while receiving a constant rate infusion of 15 percent G/W

Post-operative course

Immediately post operatively the patient did well except for anorexia and low grade fever attributed to a urinary tract infection. Hyperglycemia was controlled with small amounts of regular insulin. On the 10th post operative day she developed nausea, abdominal pain and fullness. A big mass was palpable in the epigastrium. Serum amylase rose to 216 units and upper GIS revealed the presence of a big mass displacing the stomach anteriorly compatible with a pseudo cyst. During the next 4 weeks the mass was shown to decrease in size considerably and surgery, initially postponed, was finally deferred.

Three weeks post operatively oral GTT was diabetic with fasting value of 138 mg/dL and 1 hour post glucose of 254 mg/dL. Leucine sensitivity was no longer present (Fig. 1). A tolbutamide test showed a modest decrease in glucose from 161 to 103 mg/dL

and there was an increase in IRI from 16 μ U/ml to 75 μ U/ml promptly after 10 minutes (Table 1). This encouraged us to give a 6 months therapeutic trial with sulfonylurea, in an attempt to stimulate presumably "dormant" beta cell function that could restore her glucose tolerance, but this was without success. In spite of a diet-induced weight loss of 61 pounds, 6 months later the FBS was 273 mg/dL and a repeated I.V. tolbutamide test showed no insulin reserve. During the ensuing year she was cared for by a private physician who started her on long-acting insulin. When seen by us 14 months later her fasting blood glucose was 175 mg/dL and after 24 hours without insulin it increased to 192 mg/dL. Her last 2 clinic visits showed FBS of 200 mg (9/13/79) and 160 mg/dL (11/29/79). She still complains of occasional nausea and fullness. A gastroscopy and biopsy done 11/30/78 revealed chronic gastritis.

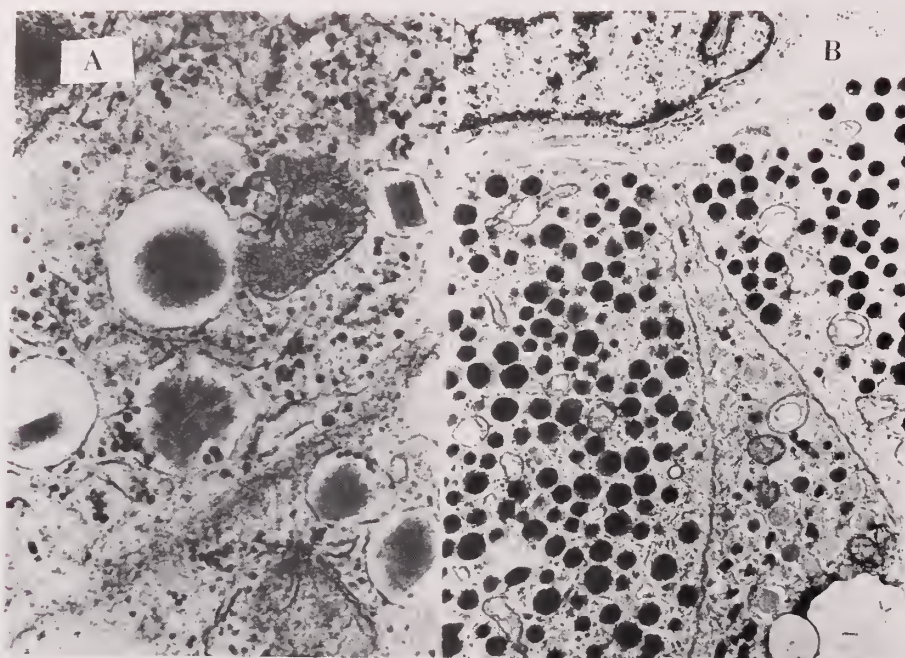


Fig. 5 A: Close-up view of beta granules in tumor (x 80,000); B: EM appearance of extra-tumora pancreatic tissue. Note alpha cell proliferation. (x25,000 reduced 1/2).

Discussion and Comments

During the past 15 years at our institution, we have screened or studied over 250 patients who have been referred for "hypoglycemia", or whose symptoms suggested a low blood glucose. Analysis of results on 183 of these patients revealed that only 10 percent fulfilled the criterion of hypoglycemia, defined as a blood glucose value of 45 mg/dL or lower (1). Among this 10 percent, the subject of the present report, has so far been the only one in whom an insulinoma has been documented. It is therefore apparent that such tumors are a rare cause of hypoglycemia. Shatney and Grage, reviewing both autopsy and case records in 18 major hospitals in the Minneapolis-St. Paul area

encountered only 27 insulinoma patients in a 40 year period (1934-73) (2). Post mortem studies suggest a prevalence of only 0.08 percent (3). We are aware of only 3 other cases in Puerto Rico (4-6) among the various institutions in the island in recent years, and the present case is the first reported insulinoma amongst our population.

The most comprehensive review of insulinomas has been carried out by Stefanini et al (7), who reported the findings on 1,067 cases from the world literature. They found a 60 percent preponderance of female sex and an age range of 4 to 82 years, with a mean of 45-1/2 years. Two thirds of patients were between 30 and 60. However, a few children under age 4 with insulinomas have been re-

ported (8, 9).

The presenting symptoms were neuropsychiatric in 92 percent of patients, comprising: loss of consciousness, sluggishness, confusion, asthenia, coma, disturbed vision and seizures. Only 11 percent had cardiovascular symptoms such as palpitations, tachycardia, precordial pain and hypertension. Gastrointestinal symptoms account only for 8.7 percent and included: hunger, vomiting and epigastric pain. It is noteworthy that fasting hypoglycemia and chronic glucopenia are thus mostly associated with neuropsychiatric symptoms. Cardiovascular and gastrointestinal symptoms, in our experience, are more often associated with the much more common acute, reactive type of hypoglycemia, not uncommonly associated with hyperventilation (1). The non-specific nature of many of these symptoms help explain delays in diagnosis. In the cited review, there was a 1 to 5 year delay in 46 percent and 20 percent had had symptoms for over 5 years. In our patient, neuropsychiatric symptoms appeared at least 8 years prior to diagnosis. In another review of 60 cases from the Mayo Clinic, the mean duration of symptoms to diagnosis was 32.5 months (10).

On physical examination, the only predominant finding is obesity, which is present in almost 50 percent of patients (7).

The diagnosis of insulinoma rests on the classical Whipple's triad (11): symptoms precipitated by fasting or exercise, hypoglycemia in association with symptoms, and relief of symptoms by food ingestion. This was fully applicable to our present report, but has been absent in many reported cases. With the advent of radioimmunoassay techniques, an additional requirement has been added: the demonstration of elevated serum or plasma levels of immunoreactive insulin (IRI). Absolute values of IRI, however, have been found to be normal in as many as 50 percent of pro-

ven insulinomas (12-14), so hyperinsulinism has been further assessed by means of so-called functional tests. These have comprised mainly excitatory stimuli such as oral glucose, intravenous tolbutamide, as well as leucine, arginine and glucagon challenges. The former 3 were well studied by Floyd et al, who confirmed previous reports that, contrary to normal subjects, tolbutamide was a more potent stimulus for insulin secretion than glucose among patients with insulinoma (14). However, the most reliable parameter turned out to be the demonstration of insulin levels that are inappropriately high for the prevailing glucose values, especially during prolonged fasting. The latter may have to be carried to 72 hours and sometimes complemented by exercise (15). In the non-fasting or after 24 hour fast, obese patients frequently have higher insulin values than normals, but this is clarified by the insulin/glucose (I/G) ratio, as these patients remain normoglycemic. Lower fasting blood glucose levels among women have been reported by Merimee et al (16), thus further complicating matters. They found that normal females had a mean glucose value of 49.6 mg/dL after a 48 hour fast, and 41.3 mg/dL after a 72 hour fast. The corresponding values for men were 74.6 and 67.5 mg/dL respectively. This has not been the experience of Service et al at the Mayo Clinic (10), who found a mean of 67 mg/dL after a 72 hour fast in 18 subjects, irrespective of sex. This important point must be clarified through the study of a larger number of patients. Our own experience would not go along with Merimee and Tyson's low values, as in most females during prolonged fasting we seldom encounter values under 52 mg/dL (1).

There are at least 3 parameters that have been proposed for evaluation of the insulin-glucose ratio. Grunt et al (17) proposed a G/I ratio of less than 2.5 as diagnostic; Fajans

and Floyd (18) suggested that an I/G ratio of over 0.3 is diagnostic, while Turner et al (19) proposed an "amended ratio" determined as: $\text{IRI} \times 100$ divided by $(\text{G}-30 \text{ mg/dL})$. Such an amended ratio is reportedly diagnostic of insulinoma if greater than 50. Service et al, however (10) found that both the $\text{G/I} < 2.5$ and $\text{I/G} > 0.3$ could miss some insulinomas, and that the "amended ratio", though decreasing the number of false-negative results, produced false positives. His experience, as well as that of Bagdade (2) favor utilizing an absolute value of IRI over $6 \mu\text{U/ml}$ (in the presence of a low blood sugar), as offering almost total discrimination of insulinoma patients. The consensus of most authors, however, seem to favor I/G ratios as more dependable, for IRI absolute values vary between laboratories as well as inter-assay.

Further diagnostic refinement has been introduced by the measurement of the insulin precursor proinsulin. Proinsulin normally contributes only 5 to 20 percent of total IRI, but can be elevated in hypokalemia, obesity and insulinomas (21, 22). The latter is particularly striking in the case of insulin-producing carcinomas (23, 24). Indeed, in the absence of hypokalemia, raised proinsulin values along with hypoglycemia are virtually diagnostic of insulinoma.

However, there can still be patients whose proinsulin levels are not over the cut-off level of 25 percent of IRI, and in whom diagnosis is not helped by excitatory tests, as these usually elevate insulin, not proinsulin, irrespective of the presence of an insulinoma (24). In such instances, suppression tests have been utilized, aiming at demonstrating failure of endogenous insulin, proinsulin, or C peptide to suppress upon the administration of purified or fish insulin (25). Sherman et al (24) found that oral diazoxide, given for 2 days, could help establish inappropriately enhanced pro-

insulin levels, as proinsulin is cleared more slowly than insulin from the circulation.

In our patient, there was a consistently high I/G ratio throughout the various tests. Especially significant was the lowering of blood glucose to 16 mg/dL , with a concomitant IRI of $38 \mu\text{U/ml}$, for an I/G of 2.37, more than 7-fold normal. Under such circumstances, no further testing was strictly indicated. However, we were interested in studying the insulin secretory pattern of this tumor and the patient's response to a therapeutic trial with diazoxide, in order to span her over the Christmas season asymptomatic, prior to her operation. Along with that, of course, we wanted to visualize radiologically the site of the tumor, which was accomplished by means of celiac arteriography.

In Stefanini's review, the most helpful technique in showing the tumor(s) preoperatively was celiac or superior mesenteric arteriography (7), as it showed 63 percent of tumors. Radioisotopic scanning, by contrast, was helpful in defining only 18 percent of cases. At the Mayo Clinic, 30 out of 34 (88 percent) of insulinomas could be localized by angiography (26). In our patient, the tumor was nicely shown at the tail of the pancreas, where it was readily found at operation. As most of these tumors are small, (40 percent are less than 1 cm and 65 percent are less than 1.5 cm) (7), CAT scanning and ultrasound are of little value (27). Our patient's tumor might have been demonstrated by CAT scanning by virtue of its location and size, but at the time of her work-up we still did not have such facilities available.

Another benefit from preoperative angiographic study is the detection of more than one tumor, present in about 10 percent of cases. In that group, there is a high prevalence of multiple endocrine neoplasia type I (7).

Treatment of insulinoma is surgical,

either by direct enucleation of identified tumors, or by partial pancreatectomy in case of multiple or larger tumors or when no tumor can be identified. One important means of assessing the adequacy of surgery is by means of intra-operative monitoring of blood glucose, as removal of the tumor(s) usually results in rebound hyperglycemia within 30 minutes. Unfortunately, this failed in our case, from lack of proper functioning of the glucose monitor. Availability of more accurate machines, such as the Biostator should prove extremely valuable in this respect at present.

First operations for insulinoma result in a cure rate of 76 percent; 16.7 percent need re-operations for cure, while in 7 percent the tumor is never found. Mortality, associated with 6 percent of first operations, rises dramatically to 18 percent during reoperations—hence the importance of proper preoperative identification and localization of tumors and careful intraoperative management. The major causes of death are acute pancreatitis (37 percent) and peritonitis (23 percent). Fourteen percent of deaths are attributable to pulmonary complications (7).

Pseudocyst formation occurs in approximately 6 percent of cases, especially among those having tumor enucleation (7). Stefanini's review fails to comment on the possible relationship of pseudocyst and the subsequent occurrence of clinically manifest diabetes mellitus. This could be considered to have been a contributing factor in our patient. Diabetes mellitus has been reported in about 10 percent of patients operated for insulinoma (7). Its occurrence seems to be related to the extent of surgery and intra-abdominal sepsis (28). In a follow-up study of 13 patients undergoing partial pancreatectomy, diabetes developed in 3, presumably due to loss of beta cell mass (2). However,

the subsequent carbohydrate tolerance of patients having had discrete tumor enucleation or less than 50 percent pancreatic resection has not been well studied. In a recent report, Ganda and Soeldner found abnormalities on 6 out of 8 such patients to a glucose challenge, but not to tolbutamide (29). None had insulin dependent diabetes. In our patient her response to tolbutamide 2 weeks post operatively (Table I), suggested she could have sufficient residual beta cell function, but a clinical trial with sulfonylureas was unsuccessful, so she had to be placed on insulin therapy. From the electron microscopy of her extra-tumoral pancreatic tissue, we know that there was a marked proliferation of alpha cells, and that the beta cell population was meager. These morphological data are in keeping with inadequate insulin reserve and her permanent diabetes mellitus.

The patient's history gave no indication or predisposition to diabetes and her family history was negative. This makes us think that her insulinoma and (or) post operative course were instrumental in her developing diabetes. One could postulate that long-term beta cell suppression could have lead to a state of "exhaustion" of these cells and that chronic hypoglycemia had induced alpha cell proliferation which brought about her diabetes. Hyperglucagonemia alone would not be expected to cause insulin-dependent diabetes, for most patients with glucagonomas are not insulin-dependent. The paucity of reports on the appearance of diabetes mellitus among patients with pseudocysts (30, 31), as well as the reversibility of such diabetes (31) would suggest that the pseudocyst per se was not the determining factor in the development of permanent diabetes in our patient, so one must decide in favor of beta cell impaired function.

Medical treatment of insulinoma patients is indicated to alleviate symptoms prior to definitive surgical therapy, when the patient is unsuitable for operation, when operative failures have occurred or in cases of malignancy. Such patients constitute 15 percent of those reviewed by Stefanini (7). The therapeutic agents used have included ACTH, glucocorticoids, glucagon-zinc, phenylhydantoin, thiazide diuretics, alloxan, streptozotocin, diazoxide and most recently, somatostatin analogs (32). Streptozotocin has been shown to produce irreversible beta cell damage that is dose-dependent, and is therefore used mainly for malignant tumors that characteristically metastasize to the liver. Diazoxide, which became available in August, 1975 as "Proglycem" is a benzothiadiazine derivative, closely related chemically to the thiazide diuretics. It had been in the market as an intravenous preparation ("Hyperstat") utilized for sudden reduction of hypertension. Although it is considered a safe drug, at least 3 cases of hyperglycemic coma have been reported with its use (33), due to excessive accumulation of the drug from concomitant renal impairment. In one autopsied case, the pancreatic islets appeared normal in spite of a total dose of 6,000 mg (33). Clinical experience suggests that oral diazoxide does not lead to irreversible beta cell destruction, rather, it inhibits insulin secretion. Its use in our patient would not appear therefore to have a pathophysiological role in causing permanent diabetes. However, among fetal sheep, goats and swine transplacental passage of diazoxide given to the pregnant mother has induced degeneration of beta cells. The reversibility of these effects was not studied (34).

From our experience with this case, and our evaluation of patients referred for "hypoglycemia" (1), it would appear that true insulinoma patients are to be looked

for among those with bizarre behaviour or neuroglycopenic-type symptoms such as could be found in neurological or psychiatric populations, rather than among those attending endocrine and general medicine clinics and wards. The latter, more often than not, will have anxiety and hyperventilation, or as it has been suggested, "non-hypoglycemia" (35).

Furthermore, we would like to emphasize the relative rarity of such tumors, and should like to discourage physicians from mentioning this far-fetched diagnostic possibility to an already anxious patient.

Acknowledgments

Dr. Tanis Robles kindly referred this patient from the Diabetes State Program. Dr. Mary Anne Rodríguez contributed in her initial work up. Dr. Constantino Pérez performed the celiac arteriography. Diazoxide (supplied as Proglycem) was kindly supplied by Dr. E. F. Wanisteker, Scherring Co. Miss Milagros Maldonado and the nursing staff at the Clinical Research Center provided expert care. Mrs. Cucha Suárez and Julia Calero provided technical and secretarial assistance respectively.

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SUPRESION DEL TIROIDES POR TRIYODOTIRONINA

José de Jesús Herrera, MD

Ocasionalmente es difícil establecer el estado funcional de la glándula en un paciente que ha estado en tratamiento por enfermedad de Graves cuyos síntomas o pruebas de gabinete son poco confiables. En estos casos las pruebas funcionales son de utilidad, como lo es la estimulación con TRH (hormona liberadora de tiotropina) o la supresión con triyodotironina (1).

Caso 1:

Paciente de 35 años de edad, sexo femenino, con historia de hipertiroidismo desde hace tres años. Se controló por año y medio con metimazole y hace año y medio está sin tratamiento. Refiere que ha disminuído la intolerancia al calor y el nerviosismo, sin embargo se queja de crisis de taquicardia y de sudoración profusa y recientemente ha perdido peso. Al examen físico, la presión arterial fue de 150/100, la frecuencia cardíaca 100/minuto. La piel es normal, ojos normales, tiroides irregular, peso aproximado 40 gramos.

Se le hace centelleo del tiroides y se determina la captación de ^{131}I en 24 horas. Centelleo del tiroides: La glándula está aumentada de tamaño. La relación de actividad de la glándula tiroides sobre el fondo y las glándulas salivares está aumentada. Cap-

tación con ^{131}I en 24 horas: 32.9 por ciento (Normal 8-35 por ciento). Después de una semana con tratamiento con triyodotironina (T_3) 25 μg tid se repiten las pruebas. Centelleo del tiroides permanece igual. Captación de ^{131}I : 36 por ciento. Conclusión: Glándula eutiroidea autónoma (Fig. 1).

Caso 2:

Paciente del sexo femenino de 32 años de edad, conocida hipertiroides desde hace dos años y bajo tratamiento con metimazole hasta hace 5 meses. Desde entonces ha estado sin tratamiento y permanece asintomática. Al examen físico se aprecia en buen estado general, la presión arterial es de 100/60 y la frecuencia cardíaca de 83/minuto. La piel es normal al igual que los ojos, el corazón con tonos cardíacos rítmicos sin soplos. El tiroides de forma y tamaño normales. Laboratorios (10 de diciembre de 1979): T_3 uptake - 33.7 (Normales 31-45 por ciento), T_4 RIA - 16.4 $\mu\text{g}/\text{dl}$ (Normales 4.5-12 $\mu\text{g}/\text{dl}$), "Free thyroxine index" 2.95. La captación de ^{131}I en 24 horas 30.8 por ciento. El centelleo del tiroides muestra la glándula ligeramente agrandada, la relación de actividad del tiroides sobre el fondo y las glándulas salivares está ligeramente aumentada (Fig. 1). Impresión: Estudio probablemente normal. El índice visual de la actividad tiroidea aumentado sugiere descartar recurrencia del hipertiroidismo. Se realiza la prueba de supresión con T_3 . La captación de ^{131}I es de 8.6 $\%$. El centelleo de tiroides muestra disminución de la relación de actividad del tiroides sobre el fondo y las glándulas salivares (Fig. 2). Impresión: Glándula tiroidea normal, no autónoma.

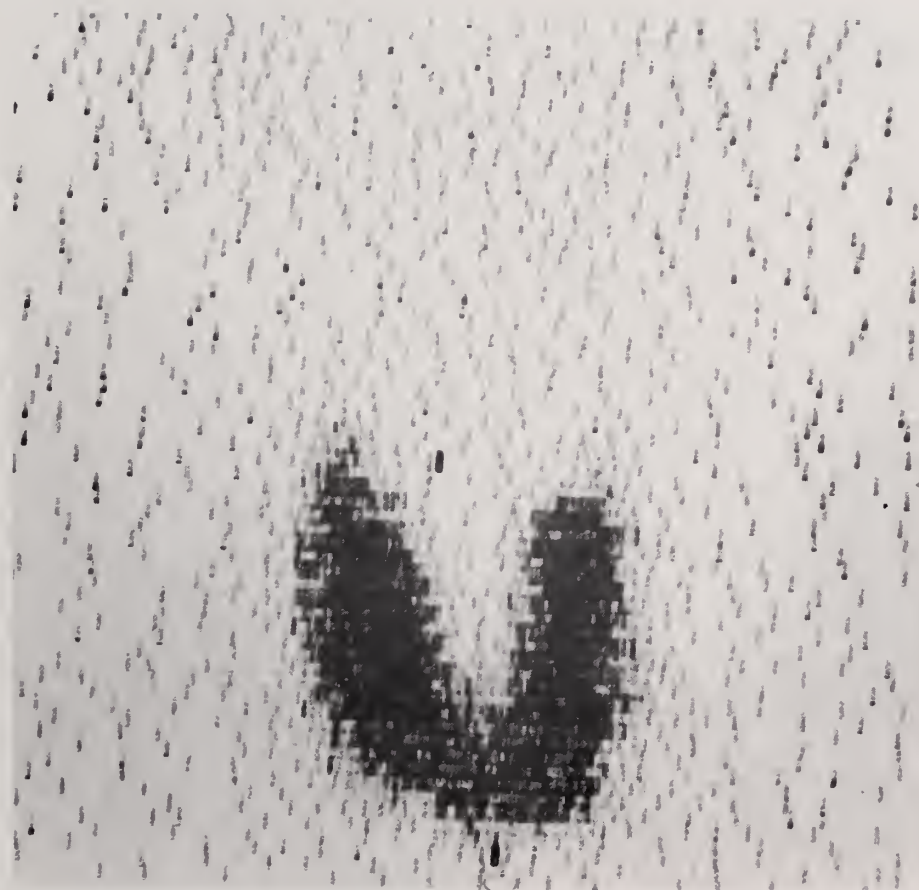


Fig. 1: Centelleo del tiroides en condiciones basales. La relación de actividad entre la tiroides sobre las glándulas salivares y el fondo está ligeramente aumentada.

Discusión

El índice visual de la captación tiroidea, "VITU" (2), estima la captación de $^{99m}\text{Tc O}_4$, pertecnetato, por la glándula tiroides. El pertecnetato es atrapado por el tiroides y glándulas salivares en relación de 2.8/1 en sujetos normales. Esta relación aumenta en sujetos hipertiroideos y disminuye en hipotiroideos.

La producción de la hormona tiroidea es controlada por el hipotálamo y la pituitaria. El hipotálamo secreta el tripéptido TRH (hor-

mona liberadora de tirotropina) en los vasos portahipofisarios, a través de los cuales alcanza la hipófisis y estimula la producción de tirotropina (TSH). La tirotropina (TSH) es el factor más importante en la estimulación aguda del tiroides a producir hormonas tiroideas. Los niveles de estas últimas influyen, a su vez, negativamente la producción de TSH. En la enfermedad de Graves, la glándula tiroides es autónoma y no depende de la estimulación de TSH para la producción de hormona tiroidea (3).

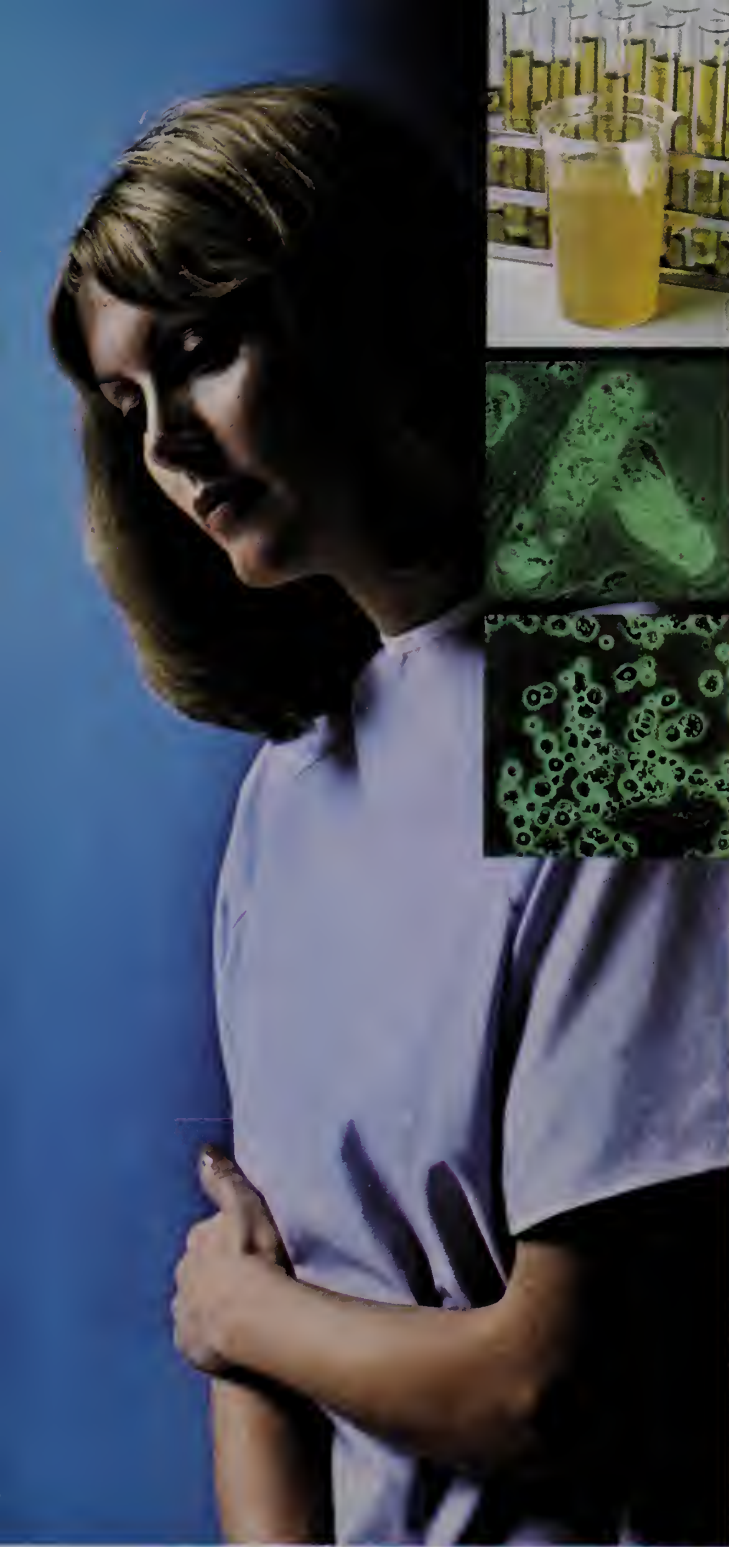


Fig. 2: Centelleo del tiroides post-supresión.
Hay disminución de la relación de actividad entre la
glándula tiroides sobre las salivares y el fondo.

La prueba de supresión inhibe la producción de TSH con hormona tiroidea exógena en sujetos normales. En sujetos con enfermedad de Graves la glándula no es suprimida.

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NOTE: Specimens for culture and susceptibility testing should be obtained prior to and during drug administration.

CONTRAINDICATIONS: Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 40 ml per minute) are contraindications to therapy with this drug. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug. For the same reason, this drug is much less effective under these circumstances.

The drug is contraindicated in pregnant patients at term as well as in infants under one month of age because of the possibility of hemolytic anemia due to immature enzyme systems (glutathione instability).

The drug is also contraindicated in those patients with known hypersensitivity to Macrochantin, Furadantin® (nitrofurantoin), and other nitrofurantoin preparations.

WARNINGS: Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin products. If these reactions occur, the drug should be withdrawn and appropriate measures should be taken.

An insidious onset of pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) in patients on long-term therapy warrants close monitoring of these patients.

There have been isolated reports giving pulmonary reactions as a contributing cause of death. (See Hypersensitivity reactions.) Cases of hemolytic anemia of the primaquine sensitivity type have been induced by Macrochantin. The hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Negroes and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Any sign of hemolysis is an indication to discontinue the drug. Hemolysis ceases when the drug is withdrawn.

Pseudomonas is the organism most commonly implicated in superinfections in patients treated with Macrochantin.

Hepatitis, including chronic active hepatitis, has been observed rarely. Fatalities have been reported. The mechanism appears to be of an idiosyncratic hypersensitive type.

PRECAUTIONS: Peripheral neuropathy may occur with Macrochantin therapy; this may become severe or irreversible. Fatalities have been reported. Predisposing conditions such as renal impairment (creatinine clearance under 40 ml per minute), anemia, diabetes, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance such occurrence.

Usage in Pregnancy: The safety of Macrochantin during pregnancy and lactation has not been established. Use of this drug in women of childbearing potential requires that the anticipated benefit be weighed against the possible risks.

ADVERSE REACTIONS: Gastrointestinal reactions. Anorexia, nausea and emesis are the most frequent reactions, abdominal pain and

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Hypersensitivity reactions: Pulmonary sensitivity reactions may occur, which can be acute, subacute, or chronic.

Acute reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or pleural effusion on x-ray, and eosinophilia. The acute reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Resolution may be dramatic.

In subacute reactions, fever and eosinophilia are observed less often. Recovery is somewhat slower, perhaps as long as several months. If the symptoms are not recognized as being drug related and nitrofurantoin is not withdrawn, symptoms may become more severe.

Chronic pulmonary reactions are more likely to occur in patients who have been on continuous nitrofurantoin therapy for six months or longer. The insidious onset of malaise, dyspnea on exertion, cough, and altered pulmonary function are common manifestations. Roentgenographic and histologic findings of diffuse interstitial pneumonitis or fibrosis, or both, are also common manifestations. Fever is rarely prominent.

The severity of these chronic pulmonary reactions and the degree of their resolution appear to be related to the duration of therapy after the first clinical signs appear. Pulmonary function may be permanently impaired even after cessation of nitrofurantoin therapy. This risk is greater when pulmonary reactions are not recognized early.

Dermatologic reactions: Maculopapular, erythematous, or eczematous eruption, pruritus, urticaria, and angioedema.

Other hypersensitivity reactions: Anaphylaxis, asthmatic attack in patients with history of asthma, cholestatic jaundice, hepatitis, including chronic active hepatitis, drug fever, and arthralgia.

Hematologic reactions: Hemolytic anemia, granulocytopenia, leukopenia, eosinophilia, and megaloblastic anemia. Return of the blood picture to normal has followed cessation of therapy.

Neurological reactions: Peripheral neuropathy, headache, dizziness, nystagmus, and drowsiness.

Miscellaneous reactions: Transient alopecia. As with other antimicrobial agents, superinfections by resistant organisms may occur with Macrochantin, however, these are limited to the genitourinary tract because suppression of normal bacterial flora elsewhere in the body does not occur.

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Smith GR et al. *Psychosomatics* 15:138, 3rd quarter, 1974

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Tobin JM et al. *Geriatrics* 25(6):122, 1970

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Bernstein JG. *Clinical Psychopharmacology*
Littleton, MA: PSG Publishing Company, 1978, p 123

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Bernstein JG. *Management of Side Effects Related to Antipsychotic Drug Therapy: An Interview*, 1978, p 12

*Although some instances of drowsiness have been reported, marked sedation is rare.

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Note: Extrapyramidal symptoms, when they occur, are readily controllable with antiparkinson drugs or dosage adjustment.

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Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL haloperidol may block its vasopressor activity and paradoxical further lowering of blood pressure may occur); (2) receiving anticonvulsant medication since HALDOL haloperidol may lower the convulsive threshold; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants. Concomitant antiparkinson medication, if required, may have to be continued after HALDOL haloperidol is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL haloperidol. When HALDOL haloperidol is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL haloperidol. FD&C Yellow No. 5 (tartrazine) may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Adverse Reactions: CNS Effects: Extrapyramidal Reactions. Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug

may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn.

Persistent Tardive Dyskinesia: Although rarely reported with HALDOL haloperidol, tardive dyskinesia may appear during or after long-term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and sometimes appear irreversible; there is no known effective treatment and all antipsychotic agents should be discontinued. The syndrome may be masked by reinstitution of drug, increasing dosage, or switching to a different antipsychotic agent.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms.

Cardiovascular Effects: Tachycardia and hypotension. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication.

Liver Effects: Impaired liver function and/or jaundice reported. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair.

Endocrine Disorders: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia and hypoglycemia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Autonomic Reactions: Dry mouth, blurred vision, urinary retention and diaphoresis. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration.

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TRATAMIENTO AMBULATORIO DEL ASMA BRONQUIAL EN LOS NIÑOS

José E. Sifontes, MD, Pedro M. Mayol, MD, Wilfredo Vélez, MD
Efraín Alicea, MD, Frank Rodríguez Martínez, MD y Juan J. Santana, MD

Resumen y Conclusiones: El asma bronquial es un problema común en los niños de Puerto Rico. El tratamiento actual de la mayoría de los mismos es insatisfactorio. La base del manejo del niño asmático es la prevención y el tratamiento precoz. La farmacoterapia moderna permite mantener a casi todos los niños asmáticos en buen estado de salud, participando activamente en las actividades sociales y educativas de su edad y creciendo y desarrollándose satisfactoriamente. El éxito del tratamiento depende de los conocimientos, destrezas y la inclinación del facultativo para dedicarle el tiempo que estos pacientes necesitan. La necesidad de que un niño asmático tenga que acudir a una sala de emergencia o de que sea hospitalizado constituye el fracaso del tratamiento del asma y un objetivo fundamental de éste debe ser evitar la hospitalización y más aún que el niño llegue al

estado asmático. La teofilina y los broncodilatadores agonistas beta son la base de la farmacoterapia y, sabiamente empleados, permiten el control de la mayoría de los niños asmáticos. Los corticosteroides deben usarse a tiempo y en dosis adecuadas en situaciones en las que el paciente no mejora pero durante períodos cortos no mayores de 4 días. Solamente en situaciones muy excepcionales deberán continuarse por períodos prolongados y, si esto se hace, debe emplearse beclometasona en aerosol o la prednisona oral en días alternos.

Se recalca que el asma en muchos de los casos, posiblemente la mayoría, no es de origen alérgico. Otros factores causantes importantes son la contaminación del aire, las infecciones respiratorias víricas, los cambios barométricos y de temperatura, el ejercicio y posiblemente los factores emocionales. La inmunoterapia del asma está rodeada de controversias e incertidumbres que limitan hacer recomendaciones sobre la misma.

Del Departamento de Pediatría, Escuela de Medicina, Recinto Universitario de Ciencias Médicas, Universidad de Puerto Rico, San Juan, Puerto Rico 00936. Auspiciado por el Centro de Pediatría Pulmonar, Programa "Development of Pediatric Pulmonary Care Personnel" (Grant No. MCT-00950-06-0, U. S. Dept. HEW, PHS, HSA, BCIS).

Actualización de trabajos presentados ante el Segundo Curso Internacional de Pediatría, Asociación Pediátrica Hondureña y Patronato Nacional de la Infancia, Tegucigalpa, Honduras, Septiembre 1977 y ante la Reunión Anual de la Asociación Médica de Puerto Rico, Noviembre 1980.

Summary and Conclusions: Bronchial asthma is a common problem among children in Puerto Rico. Present treatment in the majority of them is unsatisfactory. The basis for management of the asthmatic child is prevention and early therapy. Modern pharmacotherapy facilitates maintaining most asthmatic

children in good health, participating actively in social and educative activities of their age and growing and developing satisfactorily. The success of treatment depends upon knowledge, skills and willingness of the physician to devote to these patients the time that they require. The need of an asthmatic child for treatment in an emergency room or hospitalization represents failure of treatment of asthma. A fundamental objective of this treatment should be to avoid hospitalization and even more so to prevent status asthmaticus. Theophylline and beta agonist bronchodilators are the basic therapeutic agents and, knowledgeably employed, allow for control of the majority of asthmatic children. When the patient does not improve corticosteroids should be used promptly and in adequate dosages but for brief periods (not longer than 4 days). Only under exceptional circumstances should they be continued for prolonged periods of time, and if this is done, beclomethasone aerosol or oral prednisone (on alternate days) should be utilized.

Stressed is the fact that, in many cases, possibly in the majority, asthma is not of allergic origin. Other important factors in asthma are air pollution, respiratory viral infections, barometric and temperature changes, exercise and possibly emotional factors. Immunotherapy of asthma is surrounded by controversies and uncertainties which limit making recommendations about it.

El asma bronquial en los niños es un problema común en Puerto Rico. Hemos calculado que alrededor de 42,000 niños de edad escolar padecen de la afección en Puerto Rico y que la misma es común en los niños de edad preescolar ascendiendo a un 25 por ciento de éstos en un estudio de los niños que participaron en el programa "Head Start"

de San Juan y Cataño (1). Nuestras encuestas también han servido para verificar que el manejo ambulatorio del niño asmático es inadecuado, se caracteriza por tratamientos esporádicos con inyecciones en las salas de emergencia, sin seguimiento adecuado y con pocos esfuerzos por instaurar las medidas preventivas y el tratamiento precoz de la afección. A pesar de los progresos alcanzados en la farmacoterapia del asma todavía vemos con demasiada frecuencia niños que llegan a nuestro hospital moribundos como consecuencia del manejo incorrecto de su enfermedad.

El propósito de este trabajo es ofrecer la información actualizada sobre el manejo ambulatorio del asma bronquial en los niños a fin de evitar las hospitalizaciones y facilitarles llevar vidas normales y fructíferas.

Bergner, de la Universidad de Vermont, apunta que la incidencia y el impacto del asma en la familia se han menospreciado y que es incorrecto asumir que asma es una enfermedad de crisis la cual requiere medicamentos solamente durante los episodios agudos (2). Señala que las metas del tratamiento del asma deben ser: (a) evitar los episodios agudos que requieran visitas a las salas de urgencia o la oficina del médico, (b) evitar el rompimiento o la desorganización de la vida familiar y sus actividades y (c) restaurar la capacidad del asmático para la actividad física plena. El insiste en que los pediatras deben y pueden asumir una mayor responsabilidad por el manejo del niño asmático. Pero que esto lo pueden hacer solamente si están dispuestos a: (a) actualizar su entendimiento de los mecanismos del asma, (b) actualizar sus conocimientos de la ahora más complicada farmacoterapia del asma, (c) desechar conceptos anticuados sobre el asma, (d) dedicar el tiempo necesario a enseñarle al paciente, sus padres, o ambos lo que deben co-

nocer sobre la afección, (e) dedicar el tiempo necesario durante el seguimiento para asegurar el cumplimiento con el tratamiento continuo o intermitente, (f) dedicar el tiempo necesario durante el seguimiento a hacer los ajustes y reajustes necesarios en el programa terapéutico de acuerdo con las necesidades y tolerancia de cada paciente.

Definición: No existe una definición aprobada de asma bronquial. Numerosas comisiones lo han intentado sin llegar a un acuerdo. La "American Thoracic Society" acaba de nombrar un nuevo comité para continuar intentándolo. Nuestra definición es la siguiente: el asma bronquial es un trastorno producido por hiperreactividad de las aerovías caracterizado por obstrucción bronquial y bronquiolar debida a contracción de los músculos lisos, edema y exceso de mucosidad. Es reversible espontáneamente o por la administración de broncodilatadores. Puede estar asociada con ciertos antígenos de histocompatibilidad celular (HLA), lo que está en armonía con una susceptibilidad determinada por factores genéticos (3).

Etiología: La etiología del asma bronquial en los niños ha sido motivo de tratados y controversias. La definición que hemos esbozado en gran parte determina los factores etiológicos. En un porcentaje indeterminado el cual estimamos oscila entre 30 por ciento y 50 por ciento es probable que los factores principales sean alérgicos. En los otros se asocia con otros factores que determinan la reacción asmática. Entre éstos, pueden incluirse las infecciones respiratorias víricas, la contaminación del aire y los cambios climatológicos que traen cambios de temperatura y producen otras alteraciones del contenido de las partículas del aire, irritantes o alérgicas. La contaminación del aire es

un factor que en algunos casos ha sido responsable de epidemias de asma (4). El humo de cigarrillo es el contaminante más común en los hogares de los niños. Otros factores incluyen ejercicios rápidos y continuados como correr o jugar baloncesto y el frío, por ejemplo, entrar en un salón con aire acondicionado a temperaturas bajas (5). Los factores emocionales pueden contribuir a precipitar el acceso y al empeoramiento o persistencia del mismo.

Clasificación: El asma se ha clasificado en diferentes formas como, por ejemplo, extrínseca e intrínseca, en la que aquella es de origen alérgico y ésta de origen infeccioso u otro. También se ha clasificado de acuerdo con las diferentes etapas de progreso de la enfermedad y se ha clasificado en relación con etiologías adicionales tales como la producida por la aspirina y la relacionada con distintas ocupaciones; por ejemplo, el asma de los criadores de aves. En los niños, la más reciente del texto de Nelson de 1979, la clasifica en formas leves, moderadas y severas (3). Los criterios que utiliza esta clasificación se resumen en la Tabla I.

Es evidente que esta tabla clasifica como moderadas formas que algunas personas considerarían severas. Sin embargo, la misma permite asumir actitudes más serenas ante una afección que, por lo recurrente de la misma, puede ser causa de desesperación tanto por parte de los padres como del facultativo que atiende el niño.

Manejo del asma bronquial.

Diagnóstico correcto: El comienzo del manejo del asma es hacer el diagnóstico correcto de la enfermedad. Puede que haya historia familiar de asma o de alergia. Los síntomas de la afección a veces son típicos o

TABLA I
Clasificación del Asma en los Niños

	<i>Leve</i>	<i>Moderada</i>	<i>Severa</i>
<i>Frecuencia</i>	<i>Una vez en semana o menos</i>	<i>Una vez en semana o más</i>	<i>Sibilancias constantes. Hospitalizaciones frecuentes</i>
<i>Respuesta a broncodilatadores</i>	<i>En 24 a 48 horas</i>	<i>Responden pero los necesitan continuamente</i>	<i>Los necesitan continuamente y muchas veces por la vía parenteral o en aerosol</i>
<i>Síntomas entre ataques</i>	<i>No</i>	<i>Algunos</i>	<i>Casi todos los días</i>
<i>Medicamentos</i>	<i>Los necesitan durante los accesos solamente</i>	<i>Los necesitan casi continuamente</i>	<i>Los necesitan continuamente incluyendo en muchos casos aerosoles y corticosteroides</i>
<i>Asistencia a la escuela</i>	<i>Buena</i>	<i>Afectada</i>	<i>Muy pobre</i>
<i>Tolerancia al ejercicio</i>	<i>Buena</i>	<i>Disminuída</i>	<i>Pobre</i>
<i>Radiografía</i>	<i>Normal</i>	<i>Anormal</i>	<i>Anormal</i>
<i>Hiperaeración del tórax</i>	<i>No</i>	<i>Presente</i>	<i>Presente con deformidad</i>
<i>Trastornos de la función pulmonar</i>	<i>Leves y reversibles</i>	<i>Presentes</i>	<i>Severos</i>

la tos puede ser el único síntoma. La afección debe responder favorablemente a la epinefrina acuosa .01 ml/kg, solución 1:1000 (dosis máxima, 0.3 ml), por la vía subcutánea hasta 3 dosis a intervalos de 20 minutos.

Deben descartarse otras causas de el síndrome asmático incluyendo los trastornos cardiovasculares, los cuerpos extraños, la migración pulmonar de parásitos, la fibrosis quística del páncreas, la tuberculosis traqueobronquial,

los procesos malignos que puedan afectar el árbol traqueobronquial, las reticuloendoteliosis y otras afecciones. El trabajo de laboratorio inicial debe incluir el hemograma, la coproparasitología, el análisis de la orina, la prueba de la tuberculina y la radiografía anteroposterior y lateral del tórax. Esta puede ser normal o mostrar atrapamiento de aire, pequeñas atelectasias y acentuación de la trama. Con frecuencia se confunden estos hallazgos con bronconeumonías y se hacen radiografías repetidas innecesariamente. De gran utilidad para la evaluación inicial y continuada del paciente es la espirometría, la medición del flujo espiratorio (FEF 25-75 por ciento), o por lo menos, la medición del pico del flujo espiratorio el cual está disminuido por lo menos en 20 por ciento.

Identificación de los factores etiológicos: Parte esencial del manejo del asma es la identificación de los factores etiológicos que se han mencionado anteriormente. Para este propósito hemos elaborado el folleto "La Pesquisa de las Causas de Alergia y del Asma Bronquial" (Apéndice 1) el cual ofrece una descripción sencilla del asma y los síntomas de alergia y ofrece una lista de cotejo que los padres o encargados pueden utilizar para identificar los distintos posibles factores etiológicos. Este folleto ha sido reproducido por la Asociación Puertorriqueña del Pulmón y está disponible libre de costo en las oficinas de la misma.

Una vez que se hayan identificado posibles factores etiológicos, se hacen los intentos por eliminar los mismos. Se recalca la importancia del control del polvo casero (Apéndice II): forrar los colchones con plásticos para evitar la exposición a los ácaros; evitar la lana o pluma de aves; eliminar cortinas, alfombras, muñecos de peluche; evitar olores fuertes, abanicos polvorientos, etc.

En Puerto Rico los hongos son un factor importante. Estos son más abundantes en las casas terreras y en los sitios húmedos (6). Si hay padres fumadores se les orienta a no fumar dentro de la casa. Si aparenta haber una relación entre la ingestión de un alimento y síntomas alérgicos se elimina el mismo de la dieta por un período de 5 o 6 semanas; si el paciente mejora se administra de nuevo el alimento; si empeora se remueve de nuevo y se intenta otra vez causar los síntomas introduciendo el alimento nuevamente. Es importante no mantener pacientes en los que se sospechan alergias por alimentos en dietas restrictivas indefinidamente a menos que se haya probado sin lugar a dudas la relación de causa y efecto entre el alimento y los síntomas. Usualmente, este problema es de los primeros dos años de vida y en la mayoría de los casos los alimentos son tolerados después de la infancia.

Farmacoterapia: Actualmente la farmacoterapia adecuada es la base del tratamiento del niño asmático (7). Los medicamentos que se emplean más comúnmente son los inhibidores de la fosfodiesterasa (las xantinas-teofilinas) y los agonistas de los receptores beta (agentes simpaticomiméticos como isoproterenol, metaproterenol y la terbutalina). Una vez que se hace el diagnóstico de asma se debe dedicar el tiempo necesario a educar los padres y al niño, si este es mayor, sobre la fisiopatología de la enfermedad, la importancia de las medidas preventivas y de tomar los medicamentos a tiempo. En algunos casos más severos, se puede establecer la analogía que hay entre la necesidad del diabético de usar insulina o del cardíaco de tomar digital y del asmático de tomar teofilina u otro broncodilatador.

Las teofilinas: Las teofilinas, derivadas

TABLA II
Teofilina
Posología del Asma en el Paciente Ambulatorio *

<i>Edad</i>	<i>Mg/kg cada 6 horas, vía oral **</i>
<i>4 a 16 semanas</i>	<i>2.7 a 3.2</i>
<i>17 a 24 semanas</i>	<i>3.5 a 3.9</i>
<i>25 a 32 semanas</i>	<i>3.7 a 4.5</i>
<i>33 a 48 semanas</i>	<i>3.7 a 5.9</i>
<i>1 a 9 años</i>	<i>3.7 a 8.7</i>
<i>9 a 11 años</i>	<i>3.7 a 7.5</i>
<i>12 a 16 años</i>	<i>3.7 a 6.25</i>
<i>Sobre 16 años</i>	<i>1.7 a 5.75</i>

* - Fuente: Estas dosis se han adaptado de la información sobre cifras sanguíneas de teofilina en los infantes de 4 a 48 semanas de Nassif, E. G., et al. (*Theophylline Disposition in Infancy*, Reunión Anual Academia Americana de Pediatría, Oct. 1979) y de las cifras encontradas en los niños de 1 a 16 años por Wyatt, et al (*J Pediatr* 92: 125-130, 1978).

** - Cuando se usen preparados de larga duración como theodur, slophyllin gyrocaps, y otros de tipo "sustained release" se calcula la dosis de 24 horas empezando con las dosis más bajas/kg de peso y se administra en 2 o 3 porciones al día.

de las xantinas, son los broncodilatadores de elección en el tratamiento del asma bronquial. La absorción por la vía oral es excelente (8). Los efectos secundarios incluyen muchos parecidos a los de la xantina que más se consume, el café, incluyendo taquicardia, diuresis, gastritis y excitación. Estos síntomas pueden suceder en algunas personas con dosis adecuadas y en todas las personas cuando las dosis son excesivas. La manera ideal de controlar la dosis de teofilina es midiendo las cifras sanguíneas y administrando dosis para alcanzar niveles de 10 a 20 microgramos por mililitro. Las variaciones en las dosis se deben a variaciones en el metabolismo del fármaco y no de absorción del mismo. La dosis de teofilina varía con la edad del paciente; es

menor en los neonatos y relativamente baja hasta las 48 semanas de edad; después, aumenta la dosis por kg de peso hasta los 9 años de edad y de ahí en adelante empieza a disminuir nuevamente. Las diferentes dosis y las recomendadas para evitar entrar en dosis tóxicas se presentan en la Tabla II. Las dosis suelen administrarse en porciones cada 6 horas. La media vida de la teofilina es de 1.5 a 7.8 horas en los niños (promedio de 3.4) y de 3 a 10.8 horas en los adultos (promedio de 7.5). Se prolonga en fallo cardíaco, hepatopatías, infecciones víricas de las vías respiratorias, fiebre y con la administración de eritromicina o triacetiloleandomicina. Se acorta con tratamiento prolongado con fenobarbital, fumar cigarrillos y posiblemente por factores dieté-

TABLA III

Porcentaje de Teofilina Básica de Algunos de los Derivados de las Xantinas

<i>Aminofilina</i>	<i>85 por ciento</i>
<i>Acetato Sódico de Teofilina</i>	<i>60 por ciento</i>
<i>Glicinato Sódico de Teofilina</i> <i>(Glucofilina) (Synophylate)</i>	<i>51 por ciento</i>
<i>Oxitrifilina</i> <i>Teofilinato de Colina</i> <i>(Choledyl, Brondecon)</i>	<i>64 por ciento</i>
<i>Teofilin Monoetanolamina</i> <i>(Fleet Theophylline)</i>	<i>75 por ciento</i>
<i>Salicilato Cálcico de Teofilina</i>	<i>50 por ciento</i>

ticos. Existen preparados de larga duración de teofilina en tabletas cuya dosis se calcula a base de la requerida en 24 horas y se divide en porciones cada 8 a 12 horas. Es importante recordar que existen innumerables formas de teofilina. Algunas son sales como la oxitrifilina. La concentración de éstas no es equivalente a la de teofilina. La oxitrifilina solamente tiene un 64 por ciento de teofilina (Tabla III). La difilina (Airet y Lufyllin) no es teofilina, las cifras sanguíneas no son comparables y los datos son insuficientes para ofrecer recomendaciones específicas.

La aminofilina rectal se emplea cuando el paciente no tolera el medicamento por la vía oral. Los supositorios no se recomiendan. Es preferible usar el líquido concentrado que se administra con una jeringuilla (Somo-

phyllin, solución rectal). Esta forma de administración debe limitarse a situaciones excepcionales. La misma conlleva un riesgo importante de sobredosis. Es esencial ofrecer instrucciones de gran precisión a la madre y estar seguro de que ella las entiende para que no hayan problemas de intoxicación por dosis excesivas del medicamento.

Los agonistas de los receptores beta:
Hay dos agonistas beta disponibles para la administración por la vía oral: metaproterenol y terbutalina. (El isoproterenol no se absorbe por la vía oral). Las dosis de estos medicamentos no están tan bien establecidas como las de teofilina. El metaproterenol está disponible en aerosol, jarabe y en tabletas. Se absorbe rápidamente y su efecto dura al-

rededor de 4 horas. Los efectos secundarios incluyen taquicardia, excitación y temores. La dosis es alrededor de 1.5 a 2.4 mg/kg/24 horas en dosis divididas cada 4 o 6 horas por la vía oral (9).

La terbutalina se absorbe rápidamente por la vía oral y tiene un efecto que dura de 5 a 8 horas. Los efectos secundarios incluyen taquicardia, excitación y temores. Estos suceden por efecto directo sobre el músculo estriado y no constituyen una reacción peligrosa. La dosis es alrededor de 50 microgramos/kg/dosis. Se puede aumentar hasta 100 microgramos/kg/dosis pero dosis mayores que éstas probablemente no aumentan el efecto broncodilatador. Una dosis para un niño de 30 kg a base de estas recomendaciones sería entre 1.5 y 3 mg cada 5 a 8 horas (7). Las tabletas disponibles son de 2.5 mg y de 5 mg. Son casi insaboras y fáciles de moler y mezclar con alguna sustancia agradable al niño. La terbutalina no se ha recomendado oficialmente para niños menores de 12 años, pero existen datos y experiencias que indican que tanto ésta como el metaproterenol pueden emplearse en niños preescolares y escolares con efectos satisfactorios y sin toxicidad importante (10, 11).

Combinaciones de broncodilatadores: Es importante no emplear dos teofilinas a la vez, ya que se entra en dosis tóxicas, pero la combinación de una inhibidora de la fosfodiesterasa (teofilina) con un broncodilatador beta agonista (metaproterenol o terbutalina) administrados en dosis independientemente calculadas representa un adelanto importante en el tratamiento del asma. Cuando el efecto broncodilatador de uno de estos dos medicamentos es insuficiente, y se añade el otro, el efecto es superior al de un medicamento sólo (12). Las dosis más bajas recomendadas para cada uno de los medicamentos a veces son

insuficientes. Pero al combinarlos el efecto puede ser equivalente al de uno sólo de los medicamentos en dosis más altas. Este dato es útil cuando un broncodilatador como la teofilina produce vómitos en dosis usuales y no los produce cuando se disminuye la misma a una dosis que sería insuficiente si el medicamento se administrara sólo. Las combinaciones fijas de las teofilinas con efedrina y sedantes no se recomiendan ya que es casi imposible hacer los ajustes necesarios para ofrecer la dosis adecuada de teofilina. Pero si un enfermo lleva años bien controlado con uno de estos medicamentos no hay necesidad de quitárselo.

Medicamentos en aerosol: Los beta agonistas: isoproterenol, metaproterenol e "isoetharine" pueden administrarse por medio de la terapéutica inhalatoria. Están disponibles comercialmente en aparatos que proveen una dosis fija por cada inhalación. Estos medicamentos son útiles en los niños mayores de 5 o 6 años a quienes se les puede enseñar a hacer las inhalaciones. El método correcto de hacerlas es motivo de controversia (13). El método generalmente aceptado es hacer la inhalación desde el comienzo y durante una inspiración profunda y lenta y esperar 5 minutos antes de hacer la segunda inhalación. Las inhalaciones se pueden repetir cada 3 o 4 horas y como regla general, a menos que una de las mismas haya sido defectuosa, no se hacen más de dos inhalaciones. La aerosolterapia con nebulizadores es más eficaz, aunque presenta los inconvenientes del equipo necesario para la misma. La Tabla IV muestra las dosis de los medicamentos.

Duración del tratamiento con los broncodilatadores: El tratamiento puede ser intermitente o continuo. Se administra al primer síntoma del acceso asmático el cual es

TABLA IV

Aerosolterapia del Asma *

Medicamento	Dosis de los Medicamentos **
	Se diluyen en 5 ml de solución normal salina y se administran por nebulizador durante períodos de 15 min.
Isoproterenol (Isuprel)	0.25 ml a 0.5 ml, solución 1:200 (0.5 por ciento)
Isoetharine (Bronkosol)	0.25 ml a 0.5 ml (1 por ciento)
Epinefrina racémica (Vaponefrin)	0.25 a 0.5 ml equivalente a 2.25 por ciento de base de epinefrina

* - Se puede administrar con nebulizadores disponibles comercialmente que produzcan partículas de 1 a 5 micrometros, tales como Maximist de Mead Johnson o De Vilviss 561. No se recomienda el método de presión positiva intermitente (IPPB).

** - La frecuencia usual es cada 3 a 4 horas. Las dosis más bajas generalmente se utilizan en los niños más pequeños. La frecuencia cardíaca sirve de guía para la dosis, duración y frecuencia de la aerosolterapia. Si la frecuencia cardíaca sobrepasa 180 por minuto debe reducirse la duración de la inhalación en alrededor de un 50 por ciento y deben prolongarse los intervalos entre los tratamientos.

tos. Después que ha pasado el acceso agudo de asma el tratamiento con broncodilatadores no debe interrumpirse abruptamente. Aunque los signos físicos sean normales la función pulmonar normal probablemente no se ha restaurado. Las aerovías pequeñas tienden a permanecer obstruidas por días o semanas después del acceso agudo. Este trastorno se puede detectar (aunque no siempre) por la espirometría en lazo. Lo recomendable es continuar los broncodilatadores de 3 a 7 días después que los signos físicos pulmonares se normalizan. En ciertos casos en los que persiste el asma, es necesaria la terapéutica con-

tinua y es prudente obtener las cifras séricas de teofilina para asegurarse que la dosis de este medicamento es la adecuada. En los casos de intolerancia a la teofilina el tratamiento puede hacerse con metaproterenol o terbutalina suplementándolo (de acuerdo con la tolerancia) con teofilina.

El paciente que no mejora: Algunos pacientes no mejoran a pesar del tratamiento en dosis correctas. En estos casos es necesario identificar posibles complicaciones, las cuales incluyen bronconeumonía o bronquitis, que pueden ser de origen bacteriano por super-

infección secundaria con la flora normal de las vías respiratorias. También hay que descartar la posibilidad de atelectasias, neumotórax, neumomediastino, o de la presencia de las otras posibles causas del síndrome asmático. Es importante revisar las bases del diagnóstico de asma y asegurarse de que el mismo no está equivocado.

Tratamiento con antimicrobianos: En el asma aguda sin complicaciones bacterianas no está indicado el tratamiento con antimicrobianos. Este puede ser útil en el paciente con otitis media, sinusitis o síntomas respiratorios persistentes, particularmente tos, por infección bacteriana secundaria de las vías respiratorias bajas. Estos casos pueden tener pocas manifestaciones de infección la que puede suceder sin fiebre y sin alteraciones del leucograma. Una mejoría después de 3 o 4 días de antibióticoterapia, es sugestiva de infección bacteriana e indicación para continuar los antibióticos hasta completar por lo menos 10 días. Pueden emplearse amoxicilina, eritromicina o cefaclor. En los preescolares conviene añadir sulfisoxazole al tratamiento con eritromicina.

Tratamiento con Corticosteroides: El paciente asmático que no mejora, y la falta de mejoría no se debe a las complicaciones descritas; debe recibir un tratamiento corto, intenso y a tiempo con corticosteroides. Pueden emplearse la prednisona, la betametasona o la dexametasona. La dosis es de 2 a 3 mg/kg de prednisona por día o el equivalente de las otras formas de corticosteroides. Este tratamiento se administra por 48 horas y en algunos casos hasta 4 días pero no más de 4 días. La mayoría de estos pacientes mejoran en 24 horas y continúan bajo control con broncodilatadores sin necesidad de más corticosteroides. Pero en algunos casos, esto no es así.

Tratamientos Preventivos Continuos.

Cuando la enfermedad está incapacitando al paciente para sus funciones normales deben intentarse tratamientos preventivos continuos.

Cromolyn: En los niños mayores de 4 o 5 años se puede usar la inhalación de un estabilizador de las células cebadas para evitar la liberación de los mediadores químicos que producen la reacción asmática. Se emplea el cromolyn sódico (aarane o intal) en inhalaciones, 1 cap. de 20 mg, cuatro veces al día. Algunos pacientes pueden controlarse con inhalaciones de dos o tres caps. y otros, en los que se sabe el agente que produce el asma, se pueden emplear las inhalaciones cuando va a suceder la exposición. Por ejemplo, si la persona es alérgica al polvo y va a estar expuesta a cantidades excesivas, hace la inhalación antes de la exposición o si el asma es inducida por ejercicio la debe hacer antes de empezar el ejercicio. El cromolyn es un medicamento preventivo y no es eficaz durante el acceso asmático. Las reacciones adversas al cromolyn incluyen irritación local de la orofaringe, esofagitis, reacciones alérgicas y otras (14). Las reacciones adversas al cromolyn impiden su utilización en algunos casos. Otro impedimento es el coste del tratamiento el cual puede ascender hasta 3 o 4 dólares al día. En alrededor del 50 por ciento de los pacientes en los que se emplea el cromolyn el mismo no es efectivo. Muchas veces el fracaso se debe a que el paciente no se ha instruido correctamente sobre cómo usar el inhalador o a que emplea el medicamento teniendo broncospasmo. En estos casos, inhalaciones de metaproterenol, isoproterenol o "isoetharine" varios minutos antes de las de cromolyn facilitan la penetración de éste en los bronquios.

Corticoesteroides: Cuando el cromolyn no se puede utilizar debe considerarse la posibilidad de tratamiento con corticosteroides. La forma de elección es por medio de inhalaciones empleando la beclometasona (Vanceril). Este medicamento se absorbe en cantidades mínimas y su efecto en la supresión del eje pituitaria-adrenal es mínimo, aunque no es inexistente (15). Se recomiendan 100 microgramos (dos inhalaciones) 3 o 4 veces al día. En algunos casos es útil que éstas estén precedidas de inhalaciones de los broncodilatadores. Después de las inhalaciones de beclometasona debe instruirse al paciente para que se enjuague la boca con agua a fin de evitar la moniliasis oral que a veces es una complicación del tratamiento prolongado con beclometasona. Otra complicación que ya se ha informado es la reactivación de un foco tuberculoso pulmonar, de manera que si estos pacientes tienen la reacción positiva a la prueba de la tuberculina deben protegerse con isoniácida (16).

En los casos de niños que no sepan o puedan utilizar la beclometasona puede emplearse la prednisona en días alternos. Se utiliza la dosis mínima que permita suprimir los síntomas de asma. Usualmente, esta oscila entre 10 y 30 mg por día. Un corticosteroide nuevo, el cloprednol, tiene una media vida más corta que la de la prednisona y parece ser más eficaz que ésta para el tratamiento preventivo de asma con menor supresión del eje pituitaria-adrenal (17). En el tratamiento prolongado con corticosteroides no deben emplearse otros de media vida más larga como dexametasona, ya que los mismos afectan en forma considerable el eje pituitaria-adrenal y pueden causar interrupciones del crecimiento y otras manifestaciones tóxicas con mayor frecuencia que la prednisona.

El paciente que va a recibir corticosteroides por largos períodos de tiempo y tiene

la reacción a la tuberculina positiva, debe recibir isoniácida mientras esté recibiendo los corticosteroides y probablemente por varios meses después que el tratamiento con éstos se haya interrumpido. Todo paciente que recibe tratamiento prolongado con corticosteroides debe vigilarse cuidadosamente y en cualquier situación nueva de "stress" debe recibir los corticosteroides nuevamente. Esto es de particular importancia en el paciente que se cambia de prednisona oral a beclometasona en aerosol. El cambio debe hacerse disminuyendo la prednisona en porciones de 1.0 a 5 mg por semana durante períodos de tiempo que pueden tomar de 4 a 15 semanas. La beclometasona no es suficiente para proveerle al paciente protección en situaciones de "stress" y, si no se le administran los corticosteroides por la vía oral o parenteral cuando los necesita, el paciente puede morir. Esto ha sido el motivo de aumentos en la mortalidad por asma en pacientes tratados con beclometasona en aerosol (18).

Hospitalización: Cuando no hay respuesta al tratamiento inicial adecuado y hay dificultad respiratoria progresiva debe hospitalizarse el paciente. Las complicaciones como atelectasia, neumonía, neumotórax, neumomediastino, son señales importantes de la necesidad de hospitalización. El pulso paradójico sobre 20 mm de mercurio apunta hacia insuficiencia respiratoria inminente. El paciente asmático que se ve extremadamente intranquilo o que deja de luchar repentinamente y aparentemente mejora por signos físicos (desaparecen las sibilancias), puede que haya entrado en la insuficiencia respiratoria. El estado asmático ("status asthmaticus") es la indicación más clara para la hospitalización del paciente asmático pero es importante hacer una nueva definición del estado asmático.

Cuando el enfermo no mejora con el tratamiento adecuado se dice que se halla en el estado asmático. La antigua definición de éste era ausencia de respuesta a varias inyecciones de epinefrina. La disponibilidad de nuevos medicamentos y la nueva orientación del tratamiento han hecho que se cambie la definición.

Leffert define el estado asmático ("status asthmaticus") como la condición en que se halla el paciente cuando hay una probabilidad significativa de que la insuficiencia respiratoria vaya a suceder si no se ofrece un tratamiento pronto y enérgico (5). Los signos que deben buscarse son: la dificultad respiratoria, la deshidratación, taquicardia sobre 150/minuto, ruidos respiratorios que dejan de ser sibilantes y se tornan apagados o ausentes a pesar de gran esfuerzo respiratorio, pulso paradójico, cianosis y gran intranquilidad o estupor. Estas manifestaciones constituyen indicaciones claras para la hospitalización del enfermo.

Fisioterapia: La fisioterapia pulmonar se está empleando con frecuencia en el tratamiento del niño asmático. Se emplean drenaje postural, palmoteos, vibraciones, succión y a veces presión intermitente positiva acompañando la aerosolterapia. La fisioterapia no está indicada en la etapa aguda del asma. Después de ésta sus beneficios no están claramente establecidos. Se recomienda un ensayo de drenaje postural con palmoteos y vibraciones y de acuerdo con el resultado se continúa o se interrumpe esta forma de tratamiento. A menos que haya un beneficio claro no vale la pena continuarlo (3). En muchos casos puede administrarse por la madre del paciente después que ésta haya sido instruída sobre cómo hacerlo por el fisioterapeuta. Es de mayor beneficio cuando hay atelectasia o secreciones abundantes espesas. La aerosol-

terapia con broncodilatadores antes de la fisioterapia es beneficiosa. La presión intermitente positiva (IPPB) no se recomienda en el asma bronquial ya que puede causar neumotórax o broncospasmo (5, 19).

Hidratación: La hidratación del paciente asmático debe ser adecuada pero no excesiva. Se conoce que el agua es el mejor expectorante pero también se sabe que la sobrehidratación puede conducir a edema intersticial pulmonar y causar mayor dificultad respiratoria.

Expectorantes y Yodo: Hay duda sobre la existencia de un expectorante eficaz. Los efectos de los que se administran probablemente son más los de un placebo que de un expectorante. El yodo puede causar más problemas que los que resuelve, por sus reacciones secundarias (20). Muchos medicamentos llamados expectorantes causan irritación gástrica y vómitos y por este mecanismo pueden desalojar secreciones pero a la vez pueden hacer que el paciente se deshidrate.

Sedantes: Los sedantes pueden causar depresión respiratoria y hacer más daño que bien en el paciente asmático. Pueden confundir el cuadro e impedir la identificación de la insuficiencia respiratoria. Si es necesario emplear un sedante el de elección es hidrato de cloral, el cual no deprime el centro respiratorio. La dosis es de 25 mg/kg cada 4 a 6 horas.

Antitusivos: Hay solamente dos antitusivos eficaces: la codeína y el dextromorfan. Los mismos no deben emplearse en la mayoría de los problemas respiratorios ya que inhiben la mejor forma de expulsar las secreciones, que es la tos, y en esta forma contribuyen a la acumulación de secreciones que sirven como medio de cultivo y contribuyen a la obstrucción bronquial. De este modo propician las bronqui-

tis y bronconeumonías bacterianas y las atelectasias. Los antitusivos pueden usarse en forma esporádica para la tos improductiva, severa, que impide el descanso y la nutrición del enfermo.

Gamma globulina: La gamma globulina está indicada en los pacientes que tienen el defecto congénito o adquirido probado por mediciones cuantitativas de la inmunoglobulina gamma. Si el defecto es de inmunoglobulina A, que es el más común, la gamma globulina está contraindicada ya que no es suficiente para suplir esta inmunoglobulina y puede causar reacciones alérgicas serias. El paciente asmático que vaya a tratarse con gamma globulina debe ser evaluado cuidadosamente para asegurarse que el defecto existe y para atenderlo en forma total de acuerdo con el tipo de deficiencia inmunológica que se descubre.

Efedrina: La efedrina es un descongestionante nasal y un broncodilatador. La dosis es de 0.5 a 1 mg/kg cada 6 horas. No es tan eficaz como los beta agonistas y produce más reacciones secundarias que éstos. Puede usarse si no están disponibles el metaproterenol o la terbutalina.

Antihistamínicos: Los antihistamínicos bloqueadores de los receptores H-1 incluyen por lo menos 6 tipos reconocidos. Se aduce que están contraindicados en asma ya que secan las secreciones respiratorias, pero los estudios en pacientes asmáticos han demostrado que, si bien no producen mejoría, tampoco suelen causar efectos adversos. La excepción es el antihistamínico del grupo de las fenotiacinas (fenérgán) el cual contribuye a la broncoconstricción. Los demás no tienen efecto en el grado de broncoconstricción, exceptuando la clorfeniramina que

en dosis altas produce broncodilatación (21). Si es necesario emplear un antihistamínico por manifestaciones de rinitis alérgica, urticaria u otras es preferible utilizar clorfeniramina (Chlor-Trimeton, Teldrín).

Inmunoterapia: El tratamiento del asma bronquial con inmunoterapia es motivo de controversia. Se hace difícil la evaluación de la misma ya que en la evolución natural del asma bronquial hay mejorías espontáneas, otras causadas por medicamentos y otras por factores psicológicos. En sus estudios, Fontana, de New York University, demostró que al comparar un placebo con una vacuna los pacientes que recibieron el placebo y los que recibieron la vacuna mejoraron en forma comparable (22).

Patterson, de la Universidad de Northwestern, opina que la inmunoterapia está indicada para los alérgenos que no se pueden eludir (no de perros o gatos). Señala las dificultades de evaluar su eficacia y resume su opinión sobre los estudios que se pueden evaluar, la cual es: que en dosis adecuadas alivia la rinitis alérgica por el polen del heno; que el mecanismo de acción no está claro y que se necesitan más estudios sobre el mismo. En el asma bronquial expresa que la eficacia de la inmunoterapia es más difícil de probar dados los numerosos factores variables pero favorece la inmunoterapia de asma de "duración y síntomas significativos" causada por pólenes, hongos ("molds") y polvo cuando estos alérgenos no se pueden evitar (23).

Es probable que las fallas de la inmunoterapia se deban al gran porcentaje de pacientes en los que la etiología del asma no es alérgica, a que los alérgenos adecuados no estén disponibles y a que la selección de los pacientes para las vacunas no sea la correcta.

Elliot Ellis, Profesor de Pediatría de la Universidad de Boston, expresa en el capítulo

sobre trastornos alérgicos del texto NELSON PEDIATRICS, que un ensayo con inmunoterapia está indicado cuando existe una buena correlación entre los síntomas y la exposición al alérgeno en un paciente que no puede evitar la exposición a éste, que presenta evidencia de alergia mediada por IgE comprobada mediante pruebas cutáneas y pruebas in vitro (RAST) y que presenta síntomas incapacitantes que no sean fáciles de controlar con la farmacoterapia (3). Añade que no existen estándares de potencia para los extractos de alérgenos empleados en la inmunoterapia; muchos de los que están disponibles son lábiles; las dosis son empíricas y la duración óptima del tratamiento es desconocida. Recomendación que si no hay mejoría después de 12 a 18 meses de la inmunoterapia ésta se debe interrumpir. Advierte que las inyecciones deben administrarse en la oficina del médico, manteniendo el paciente bajo observación por 20 minutos y con todos los preparativos para tratar choque anafiláctico. En cuanto a los beneficios de la inmunoterapia, aduce que hay poca evidencia de los mismos. Parece mejorar la rinitis alérgica por el heno pero no el asma que éste produce. Es posible que produzca alguna mejoría en la alergia al polvo y los pólenes de yerbas pero no hay evidencia de que sea efectiva en las alergias a hongos, bacterias, alimentos o caspa de animales. La excepción es un nuevo extracto de la caspa del gato (24). La inmunoterapia con el antígeno del veneno de himenóptera parece ofrecer protección contra el choque anafiláctico producido por la picadura del insecto, pero el beneficio de ésta en relación con el riesgo de las reacciones a la inmunoterapia ha sido cuestionado (25).

Rubenstein, de la Clínica de Alergia de la Universidad de Harvard, ha recalcado que no hay evidencia de que la inmunoterapia de la rinitis alérgica evite el desarrollo de asma

bronquial (25).

Leffert, de la Universidad de Colorado, deplora los referidos innecesarios a los alergistas para el tratamiento de asma y el concepto equivocado de que la tarea de éstos consiste principalmente en hacer pruebas de alergia y poner vacunas (26).

La situación actual ha planteado la necesidad de elaborar estándares para los extractos de alérgenos comparables a los empleados para otras drogas y productos biológicos (27). Mientras tanto, las dos alternativas que estudia la FDA ("Food and Drug Administration") son permitir solamente el uso de los alérgenos que se pueden estandarizar como algunos pólenes. Esto eliminaría del mercado la mayoría de los alérgenos y sería un paso drástico. La otra alternativa sería permitir temporalmente la utilización de todos los extractos de alérgenos que contienen antígenos para los cuales se pueda demostrar la producción de IgE en el hombre. Esta sería una medida temporal hasta que se probara que los mismos son seguros y eficaces.

Lichtenstein, Profesor de la División de Inmunología Clínica de la Universidad de Johns Hopkins, expresa que el asma es una enfermedad pulmonar que en muchos casos no es de etiología inmunológica y por ende no se beneficiarían de la inmunoterapia (28). En cuanto a esto, opina que la eficacia de la misma (excepto con ciertos pólenes) no se ha probado y que se deben hacer los estudios bien fiscalizados para evaluarla.

Weiss y Segal han señalado la necesidad imperiosa de un estudio, que en su opinión todavía no se ha hecho, sobre la eficacia de la inmunoterapia de asma alérgica, diseñado en forma doble ciega con casos testigos adecuadamente seleccionados, empleando mediciones objetivas de las sensibilidades bronquiales y celulares, de los anticuerpos de blo-

queo y reagénicos y de los síntomas mediante sistemas cuantitativos (29).

Aspectos psicosociales: De fundamental importancia es la atención a los aspectos psicosociales del niño asmático. Esto incluye planear el tratamiento en tal forma que sus actividades sociales, recreativas y educativas no se interrumpan y que el niño pueda crecer y desarrollarse física y emocionalmente en la forma más normal posible. Muchas veces es preferible dejarlo participar en un deporte o en una actividad que podría provocarle el acceso de asma y prevenir el mismo con medicamentos. El ejercicio debe estimularse. Cuando el ejercicio rápido provoca el acceso de asma las alternativas son darle un tratamiento que evite el acceso (Cromolyn, metaprotenerol o terbutalina) o recomendar un ejercicio que no provoque el asma. Por ejemplo, la natación o el "baseball" en los que la actividad no es la rápida y sostenida que provoca el asma. La educación de los padres, los maestros y otros relacionados con el niño es de gran importancia para evitar que éstos, por medio de sus acciones y gestos, le causen al niño la incapacidad psicológica.

Manejo de los problemas emocionales: El manejo de los problemas emocionales está basado en la identificación de los problemas psicológicos subyacentes (30).

Se reconocen, por lo menos, cuatro formas en las que los factores psicológicos pueden hacer que las manifestaciones del asma aparezcan o empeoren:

1. El ataque empieza cuando el paciente tiene una profunda experiencia emotiva o el ataque es precipitado por el mismo temor del paciente de que le va a dar asma.

2. El ataque está relacionado con una experiencia emotiva indirectamente; ya sea porque el paciente se agite en exceso o porque interrumpa su tratamiento.
3. El paciente se rebela contra las restricciones impuestas por el tratamiento médico: puede que sepa que es alérgico a los perros, a propósito juega con éstos, y le da el asma.
4. El paciente desarrolla el acceso de asma por razones que no tienen que ver con sus emociones pero la forma en que él, o los que lo rodean, reaccionan hace que el paciente empeore. Las causas más comunes son el miedo y la angustia en el enfermo, sus familiares o ambos.

Las primeras dos formas son raras; la tercera y cuarta son comunes. El manejo de la primera consiste en propiciar el relajamiento del paciente. En la segunda forma es necesario enseñarle a expresar sus sentimientos en formas que no desencadenen el episodio de asma. En la tercera forma hay que buscar alternativas que no afecten al enfermo y que le permitan desahogarse. En la cuarta forma hay que educar al enfermo y sus familiares para ayudarlos a reaccionar con serenidad al ataque asmático. El manejo de los factores etiológicos descritos u otros que puedan encontrarse consiste en identificarlos y substituir patrones positivos de conducta que permitan al enfermo ayudarse a sí mismo.

APENDICES:

Apéndice I - La Pesquisa de las Causas de Alergia y del Asma Bronquial.
Folleto distribuido por la Asocia-

ción Puertorriqueña del Pulmón,
Apartado de Correos 3468, San
Juan, Puerto Rico 00936.

Apéndice II - El Control del Polvo Ca-
sero. Disponible en el Centro
de Pediatría Pulmonar, Hospital
Universitario de Niños, Apartado
5067, San Juan, Puerto Rico
00936.

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MEDI-QUIZ-CARDIOLOGIA PEDIATRICA RESPUESTAS:

- 1) E. Solo en un 6 por ciento de las cardiopatías congénitas se conocen factores causales. Entre las más frecuentes se encuentran las tres alternativas de la pregunta. Además de estas, algunos medicamentos como la talidomida, la difenilhidantoína y los antagonistas del ácido fólico desempeñan algún rol en la etiología de las cardiopatías congénitas.

Ref: *Current Problems in Ped.* 7 (7): 4, 1977.

- 2) D. Los soplos cardíacos son rara vez de ayuda en el diagnóstico diferencial de los neonatos con cardiopatías críticamente enfermos, ya que muchas veces no tienen soplo. Es según el niño crece que los soplos asumen las características que nos permiten hacer clínicamente un diagnóstico anatómico.

Ref: *Current Problems in Congenital Heart Disease*, Spectrum Publications, New York, 1979, p. 22.

- 3) E. Las indicaciones más frecuentes para estudios diagnósticos invasivos en niños con cardiopatías congénitas son: fallo cardíaco que no responde al tratamiento; cianosis persistente, y en cardiopatías en que su historia natural desfavorable es conocida. También se indican en el período post operatorio para evaluar los resultados de la cirugía, determinar la presencia o ausencia de defectos residuales, y evaluar el status funcional car-

díaco.

Ref: *Pediat. Clin., North Am.* 25 (4): 707, 1978

- 4) B. Los defectos interventriculares pequeños no requieren reparación quirúrgica ya que en ellos la carga hemodinámica es pequeña y el riesgo quirúrgico es mayor que el del curso natural de un defecto pequeño.

Ref: *Pediat. Clin., North Am.* 25(4): 749, 1978

- 5) C. La miocardiopatía hipertrófica obstructiva es una enfermedad del músculo cardíaco que se transmite de una forma autosómica dominante. Se caracteriza por un engrosamiento marcado del septo interventricular, cambios electrocardiográficos y movimiento anormal de la valva anterior mitral. Esta miocardiopatía usualmente no se manifiesta clínicamente hasta la segunda o tercera década de vida.

Ref: *Current Problems in Congenital Heart Disease*, Spectrum Publications, New York, 1979, p. 143.

- 6) B. En pacientes con esta miocardiopatía donde no se ha demostrado obstrucción al tracto de salida deben tratarse con agentes bloqueadores betaadrenérgicos para reducir el consumo de oxígeno por parte del ventrículo hipertrófico. Cuando está indicada la cirugía el procedimiento de elección es la ventriculomiotomía transaórtica y si hay afectación mitral ésta debe reemplazarse.

Ref: *Current Problems in Congenital Heart Disease*, Spectrum Publications, New York, 1979, pp. 162-163.

- 7) E. Las técnicas diagnósticas de ultrasonido se han desarrollado como un método seguro e incruento para el diagnóstico de cardiopatías congénitas. Se han analizado extensamente los aspectos morfológicos septales y valvulares así como las medidas cualitativas y cuantitativas de las cámaras cardíacas.

Ref: *Current Problems in Congenital Heart Disease*, Spectrum Publications, New York, 1979, p. 105.

- 8) E. Hay evidencia reciente favoreciendo el inicio de las lesiones ateroscleróticas en la edad pediátrica. Se han llamado factores de alto riesgo a algunas condiciones cuya presencia va asociada con una incidencia de aterosclerosis sobre el nivel del promedio. Estos factores son: la hiperlipidemia, la hipertensión, y el hábito de fumar. Otros factores son: la obesidad, la hiperglucemia, el hábito sedentario y la tensión sicosocial.

Ref: *Current Problems in Ped., Year Book Med.*

Pub., 7 (7): 30, 1977.

- 9) A. En niños con historial previo de fiebre reumática la incidencia durante períodos de infecciones por estreptococo es de 16 por ciento. En la población general la incidencia es de solo 3 por ciento durante períodos epidémicos de infecciones estreptocócicas.

Ref: *Current Problems in Ped., Year Book Med. Pub.*, 7 (7): 22, 1977.

- 10) A. En el fenómeno de Wenckebach (Mobitz I) hay un aumento progresivo del intervalo P-R que culmina en el bloqueo de una contracción atrial sin respuesta ventricular. También hay un acortamiento progresivo del intervalo R-R, tiene mejor pronóstico que el Mobitz II, y puede verse en atletas normales. Este bloqueo de 2º representa un trastorno de conducción que puede producirse aún en un corazón normal con una frecuencia atrial rápida o un tono vagal aumentado.

Ref: *Pediat. Clin., North Am.* 25 (4): 881, 1978.



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Also highly effective against roundworm and hookworm

Since whipworm, roundworm and hookworm are all soil-borne helminths, mixed infections are not uncommon. Only one anthelmintic exhibits high efficacy rates for all three nematodes: whipworm—68%; roundworm—98%; hookworm—96%. That agent is VERMOX[®].

Please see following page for Summary of Prescribing Information.

Broad-spectrum coverage in mixed helminthic infections

Vermox[®] TABLETS
(mebendazole)



JANSSEN PHARMACEUTICA INC.
New Brunswick, N.J. 08903

Committed to research...
because so much remains to be done.

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JPI-023



**Broad-spectrum
coverage in mixed
helminthic infections**

Ver[®]mo[®]x
TABLETS
(mebendazole)

Contraindications VERMOX is contraindicated in pregnant women (see: Pregnancy Precautions) and in persons who have shown hypersensitivity to the drug.

Precautions **PREGNANCY:** VERMOX has shown embryotoxic and teratogenic activity in pregnant rats at single oral doses as low as 10 mg/kg. Since VERMOX may have a risk of producing fetal damage if administered during pregnancy, it is contraindicated in pregnant women.

PEDIATRIC USE: The drug has not been extensively studied in children under two years; therefore, in the treatment of children under two years the relative benefit/risk should be considered.

Adverse Reactions Transient symptoms of abdominal pain and diarrhea have occurred in cases of massive infection and expulsion of worms.

Dosage and Administration The same dosage schedule applies to children and adults. The tablet may be chewed, swallowed or crushed and mixed with food. For the control of pinworm (enterobiasis), a single tablet is administered orally, one time.

For the control of roundworm (ascariasis), whipworm (trichuriasis), and hookworm infection, one tablet of VERMOX is administered, orally, morning and evening, on three consecutive days.

If the patient is not cured three weeks after treatment, a second course of treatment is advised. No special procedures, such as fasting or purging, are required.

* Mean cure rate of VERMOX[®] in treating whipworm; cure rate range of 61-75%. Data on file at Janssen Pharmaceutica Inc.

** Mean egg reduction of VERMOX[®] in treating whipworm; egg reduction range of 70-99%. Data on file at Janssen Pharmaceutica Inc.

† Rollo, I.M.: Drugs used in the chemotherapy of helminthiasis, in Goodman, L.S.; and Gilman, A. (eds.): *The Pharmacological Basis of Therapeutics*, ed. 5. New York, Macmillan, 1975, p. 1034.

†† Miller, M.J.; Krupp, I.M.; Little, M.D.; Santos, C.: Mebendazole an effective anthelmintic for trichuriasis and enterobiasis. *JAMA* 230 (10): 1412-1414, Dec. 9, 1974.

1. Registered trademark of Merck Sharp and Dohme.
2. Registered trademark of Roerig.
3. Registered trademark of Parke-Davis.



JANSSEN PHARMACEUTICA INC.
New Brunswick, N.J. 08903

*Committed to research...
because so much remains to be done.*

CARDIOLOGIA PEDIATRICA: LA DECADA DEL 80

La Cardiología Pediátrica ha comenzado su tercera década. Los más jóvenes en esta especialidad hemos leído de los avances logrados en la década del 50 por medio del cateterismo cardíaco y la angiocardiógrafa. Pudimos palpar en la década del 60 como la cirugía cardiovascular se realizaba con éxito en el infante y el neonato, y luego en los años 70 ya evidenciamos el desarrollo acelerado de los medios diagnósticos no-invasivos, especialmente la ecocardiografía. En la década del 80 se vislumbran progresos mayores, tanto en el mejoramiento de las técnicas diagnósticas no-invasivas y en el tratamiento farmacológico de cardiopatías congénitas, como en la cirugía, donde se perfeccionarán métodos y técnicas que permitirán una sobrevivencia mayor de niños con cardiopatías hasta hace poco inoperables.

Sin embargo, debemos admitir que no se ha logrado un progreso similar en la prevención primaria de las enfermedades cardíacas en los niños, principalmente en lo que respecta a la aterosclerosis y la hipertensión. Estas dos condiciones son hoy en día las causas más comunes de muerte en los países industrializados y se sospecha fuertemente que tengan su origen en la niñez.

La aterosclerosis es una enfermedad de las arterias en cuyas paredes ocurren depósitos grasos, los cuales sufren una serie de cambios que finalmente pueden conducir a la obstrucción total del vaso. La evidencia acumulada de material de autopsias, de estudios epidemiológicos, y de experimentos animales sugieren que la lesión aterosclerótica comienza en la edad Pediátrica, que sigue un curso progresivo en las tres primeras décadas de vida, y que luego conduce a complicaciones isquémicas y obstructivas en el adulto. (1) Tanto es así que se estima que uno de cada 5 niños varones en los Estados Unidos de Norteamérica desarrollará enfermedad de las arterias coronarias antes de los 60 años de edad. (2)

Por otro lado, la hipertensión arterial ha despertado un gran interés en los investigadores y se ha sugerido la posibilidad que la entidad conocida como "hipertensión esencial" tenga sus orígenes en la edad pediátrica y que podríamos lograr un mejor entendimiento de su etiología y patogenia estudiándola preferiblemente en niños que en los adultos ya con hipertensión "fija". La incidencia actual de la hipertensión en niños y adolescentes se desconoce con certeza, pero hay data disponible indicando que de un uno a un once por ciento de ellos tienen hipertensión. (3)

Existe la convicción de que tanto la aterosclerosis como la hipertensión vienen determinadas por una interacción compleja de factores genéticos, fisiológicos, ambientales y nutricionales. Por eso, en la medida en que vayan aumentando los conocimientos de la epidemiología, la patogenia, y la his-

toria natural de estos procesos, el Pediatra tendrá la oportunidad de ocupar una posición ventajosa para lograr la identificación temprana de aquellos pacientes de alto riesgo, e intentar evitar el origen de estos trastornos en los niños.

Por estas razones nos vemos obligados a hacer un llamado especial tanto a aquellos compañeros que tienen el privilegio de dedicar la totalidad de su tiempo y sus conocimientos a la formación de nuevos médicos, como a los que cada día se esfuerzan por hacer lo mismo con aquellos que han decidido especializarse en Pediatría o en Cardiología. Si importante es enfatizar el tratamiento de estas condiciones una vez se han manifestado clínicamente, más importante es recordar la responsabilidad que tenemos, principalmente los que trabajamos con enfermedades del corazón, de darle un mayor énfasis a la prevención primaria del proceso aterosclerótico y la hipertensión en los niños. Es necesario elaborar programas que resalten la importancia y despierten el interés tanto en la prevención primaria como en la identificación de los jóvenes de alto riesgo de padecer estas enfermedades que resultan en tantas muertes prematuras.

La posibilidad de que los comienzos de estas enfermedades en el adulto ocurran silenciosamente en niños, y que el potencial para su prevención sea una realidad, constituye un reto para todos. Este reto debemos asumirlo los Cardiólogos, los Pediatras, y sobre todo los Cardiólogos Pediátricos, en esta nuestra tercera década de existencia.

*Rafael Villavicencio, MD
Prof. Auxiliar de Pediatría
Escuela de Medicina
Universidad de Puerto Rico*

Referencias

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QuinammTM

AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

INDICATIONS: For the prevention and treatment of nocturnal recumbency leg muscle cramps, including those associated with arthritis, diabetes, varicose veins, thrombophlebitis, arteriosclerosis, and static foot deformities.

CONTRAINDICATIONS: Because of the quinine content, Quinamm is contraindicated in women of childbearing potential, in pregnancy, in patients with known quinine sensitivity, and in patients with glucose-6-phosphate dehydrogenase deficiency. Hemolysis (with the potential for hemolytic anemia) has been associated with a G-6-PD deficiency in patients taking quinine.

PRECAUTIONS: Thrombocytopenic purpura may follow the administration of quinine in highly sensitive patients. Recovery will follow withdrawal of the medication.

Cinchona alkaloids, including quinine, have the potential to depress the hepatic enzyme system that synthesizes the vitamin K-dependent factors. The resulting hypoprothrombinemic effect may enhance the action of warfarin and other oral anticoagulants.

ADVERSE REACTIONS: Aminophylline may produce intestinal cramps in some instances, and quinine may produce symptoms of cinchonism, such as tinnitus, dizziness, and gastrointestinal disturbance. If ringing in the ears, deafness, skin rash, or visual disturbances occur, the drug should be discontinued.

DOSAGE AND ADMINISTRATION:

1 tablet upon retiring. When necessary, 1 additional tablet may be taken following the evening meal.

Product Information as of September, 1977

U.S. Patent 2,985,558

Merrell

MERRELL-NATIONAL LABORATORIES Inc.
Cayey, Puerto Rico 00633

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for Knotts in the night



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each tablet contains quinine sulfate 260 mg., aminophylline 195 mg.

specific therapy for painful night leg cramps

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Each tablet contains: aspirin, 325 mg; plus codeine phosphate in one of the following strengths:
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Research Triangle Park
North Carolina 27709

MEDI-QUIZ: CARDIOLOGIA PEDIATRICA

Selecione la mejor contestación

- 1) Cuál o cuáles de los siguientes se consideran factores causales en la etiología de cardiopatías congénitas:
- a) infección materna por el virus Cocksackie B
 - b) alcoholismo materno
 - c) infección por el virus de Rubella en el primer trimestre del embarazo
 - d) solo *a* y *c* son correctas
 - e) todas las anteriores son correctas (*a*, *b*, *c*)
- 2) Cuál de los siguientes tiene *menor* valor en el diagnóstico diferencial del neonato críticamente enfermo con una cardiopatía congénita:
- a) cianosis
 - b) fallo cardíaco congestivo
 - c) alteraciones radiográficas en la silueta cardíaca y/o la vascularidad pulmonar
 - d) soplo cardíaco
 - e) alteraciones en el PO_2 , PCO_2 , y pH arterial
- 3) Algunas de las indicaciones para llevar a cabo estudios diagnósticos invasivos en niños con cardiopatías congénitas son:
- a) fallo cardíaco refractario al tratamiento médico
 - b) para evaluar los resultados de la cirugía cardíaca
 - c) en presencia de cianosis persistente o progresiva
 - d) solo las alternativas *a* y *c* son correctas
 - e) todas las alternativas son correctas (*a*, *b*, *c*)
- 4) Cuál de las siguientes cardiopatías congénitas no requiere reparación quirúrgica:
- a) tetralogía de Fallot
 - b) comunicación interventricular pequeña
 - c) ducto arterioso patente
 - d) estenosis valvular aórtica
 - e) transposición de los grandes vasos.
- 5) Cuál de las siguientes aseveraciones es incorrecta con relación a la miocardiopatía hipertrófica obstructiva en niños:
- a) está genéticamente determinada
 - b) demuestra ondas "q" profundas y cambios en el segmento ST y onda T
 - c) usualmente se manifiesta en la infancia
 - d) hay hipertrofia marcada del septo interventricular
 - e) movimiento ecocardiográfico anormal de la valva anterior mitral

- 6) Cuál de los siguientes *no* forma parte del tratamiento de la miocardiopatía hipertrófica en niños.
- a) bloqueadores beta-adrenérgicos
 - b) digoxín
 - c) ventriculomictomía
 - d) reemplazo mitral post ventriculomictomía
 - e) restricción del ejercicio
- 7) Cuál de los siguientes datos puede evaluarse ecocardiográficamente en los pacientes con cardiopatías congénitas:
- a) presencia, movimiento, y relación anatómica de los septos
 - b) las dimensiones relativas de las cámaras cardíacas
 - c) la presencia y movimiento de las válvulas atrio-ventriculares y semilunares
 - d) solo *a* y *c* son correctas
 - e) todas las alternativas son correctas (*a*, *b*, *c*)
- 8) Algunos factores de alto riesgo que aumentan la incidencia de aterosclerosis en la edad pediátrica son:
- a) hiperlipidemia
 - b) obesidad
 - c) hipertensión arterial
 - d) hiperglucemia
 - e) todas las alternativas son correctas
- 9) La incidencia de fiebre reumática en la población general durante epidemias de infecciones por estreptococo es:
- a) 3 por ciento
 - b) 30 por ciento
 - c) 16 por ciento
 - d) mayor que las alternativas anteriores
 - e) desconocida
- 10) Cuál de las siguientes aseveraciones relacionadas con la arritmia de Wenckebach (Mobitz I) en niños es incorrecta:
- a) hay un bloqueo de la contracción atrial con respuesta ventricular
 - b) hay una prolongación progresiva del intervalo P-R
 - c) hay un acortamiento progresivo del intervalo R-R luego del latido ventricular ausente
 - d) puede encontrarse en atletas normales
 - e) es patológica pero conlleva un mejor pronóstico que el Mobitz II

Rafael Villavicencio, MD
Prof. Auxiliar de Pediatría
Recinto Ciencias Médicas
Universidad de Puerto Rico

MEDI-QUIZ – INFECTIOUS DISEASE

- 1) A 22-year-old woman developed an acutely swollen, hot, tender right knee and a few pustular lesions on her fingertips. Examination of synovial fluid showed 120,000 white blood cells per cu. mm., 98 percent being polymorphonuclear leukocytes. ASO titer was 60 Todd units. Of the following, which diagnosis is most likely?:
 - a) Gouty arthritis
 - b) Rheumatoid arthritis
 - c) Gonococcal arthritis
 - d) Systemic lupus erythematosus (SLE)
 - e) Rheumatoid arthritis
- 2) The lymphocutaneous form of sporotrichosis of ten responds to treatment with
 - a) Gentamicin
 - b) Ancovon
 - c) Potassium iodide
 - d) Ampicillin
 - e) Flagyl
- 3) Acute hematogenous osteomyelitis is in most cases caused by:
 - a) Bacteroides fragilis
 - b) Salmonella typhi
 - c) Staphylococcus aureus
 - d) Streptococcus
 - e) Proteus mirabilis
- 4) In which of the following clinical situations chloramphenicol not be used:
 - a) Bacteroides fragilis infection
 - b) Staphylococcal cellulitis
 - c) Symptomatic salmonella infections
 - d) Haemophilus influenza meningitis not responding to ampicillin
 - e) Severe rickettsial infections
- 5) All of the following antimicrobial agents have primarily bacteriostatic properties, except:
 - a) Low dose streptomycin in acid medium
 - b) Demeclocycline
 - c) Penicillin
 - d) Chloramphenicol
 - e) Tetracycline
- 6) The symptom(s) which distinguish(es) botulism from other types of food poisoning is (are):
 - a) nausea or vomiting
 - b) visual disturbance
 - c) fever
 - d) arthralgia
 - e) a and b
- 7) While on a trip, a person develops nausea, vomiting, and diarrhea about 4:00 a.m., after having eaten dinner between 7 and 8 p.m. No blood or leukocytes are seen in the stool when stained with methylene blue. The most likely causal agent is:

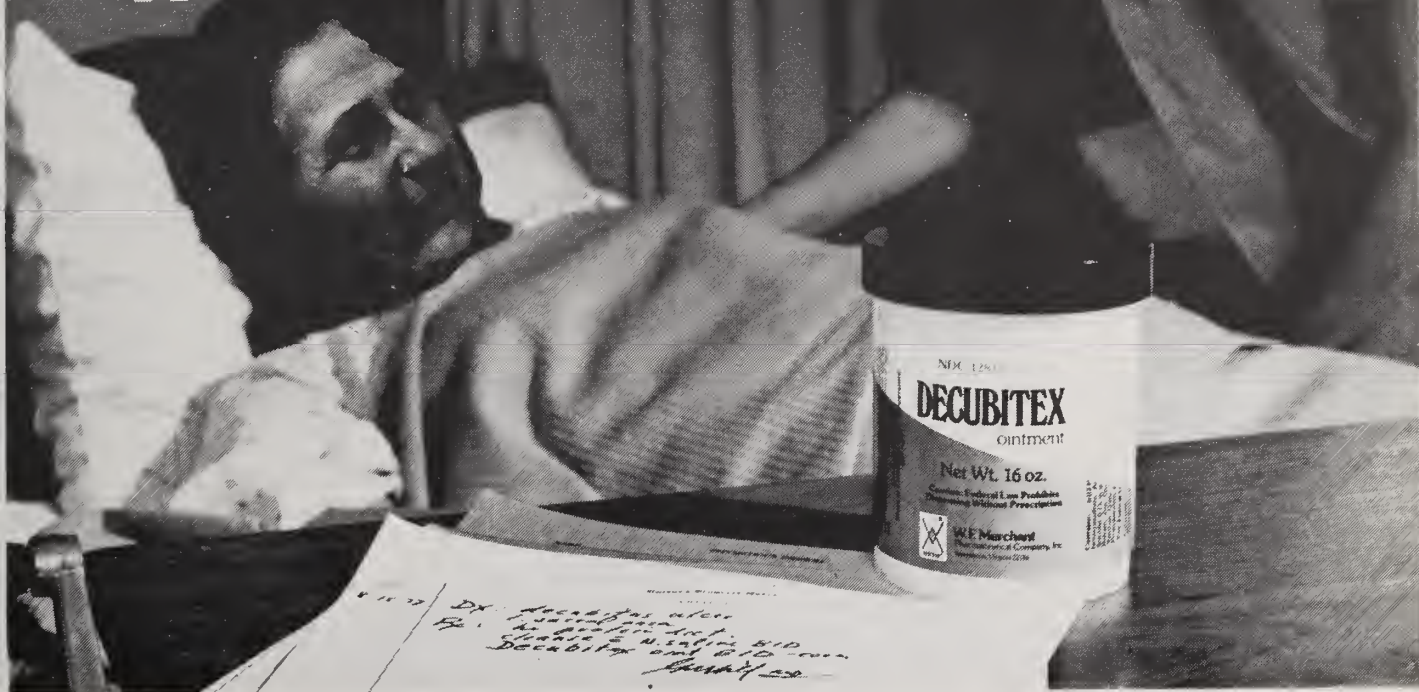
- a) staphylococcus aureus
b) salmonella
c) toxigenic E. coli
d) invasive E. coli
e) campylobacter fetus
- 8) The long half-life of the aminoglycosides in tissue indicates a particular need for determining plasma:
- a) trough levels
b) peak levels
c) MIC (minimum inhibitory concentrations)
d) toxic levels
e) all of the above
- 9) The most likely pathogen in acute bacterial prostatitis is:
- a) Escherichia coli
b) Proteus mirabilis
c) Pseudomonas sp.
d) Klebsiella sp.
e) Staphylococcus aureus
- 10) The following characterize acute bacterial prostatitis except:
- a) Chills and fever
b) Urinary urgency and frequency
c) Normal or boggy prostate on rectal examination
d) Variable obstructive voiding symptoms
e) Associated cystitis

Ramón H. Bermúdez, MD
Hospital de Veteranos
San Juan, P. R.

(Contestaciones en página 495)

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Sluggishness of
the Bowels



Constipation



Chronic
Constipation



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Perdiem™

Prescribing Information

ACTIONS: Perdiem™ with its gentle action, does not produce disagreeable side effects. The vegetable mucilages of Perdiem™ soften the stool and provide pain-free evacuation of the bowel. Perdiem™ is effective as an aid to elimination for the hemorrhoid or fissure patient prior to and following surgery.

COMPOSITION: Natural vegetable derivatives. A unique blend of psyllium and senna (Plantago Hydrocolloid with Cassia Pod Concentrate).

INDICATION: For relief of constipation.

PATIENT WARNING: Should not be used in the presence of undiagnosed abdominal pain. Frequent or prolonged use without the direction of a physician is not recommended. Such use may lead to laxative dependence.

DIRECTIONS FOR USE—ADULTS: Before breakfast and after the evening meal, one to two rounded teaspoonfuls of Perdiem™ granules should be placed in the mouth and swallowed with a full glass of warm or cold beverage. Perdiem™ granules should not be chewed. After Perdiem™ takes effect (usually after 24 hours, but possibly not before 36-48 hours), reduce the morning and evening doses to one rounded teaspoonful. Subsequent doses should be adjusted after adequate laxation is obtained.

IN OBSTINATE CASES: Perdiem™ may be taken more frequently up to two rounded teaspoonfuls every six hours.

FOR PATIENTS HABITUATED TO STRONG PURGATIVES: Two rounded teaspoonfuls of Perdiem™ in the morning and evening may be required along with half the usual dose of the purgative being used. The purgative should be discontinued as soon as possible and the dosage of Perdiem™ granules reduced when and if bowel tone shows lessened laxative dependence.

FOR COLOSTOMY PATIENTS: To ensure formed stools, give one to two rounded teaspoonfuls of Perdiem™ in the evening with warm liquid.

DURING PREGNANCY: Give one to two rounded teaspoonfuls each evening.

FOR CLINICAL REGULATION: For patients confined to bed, for those of inactive habits, and in the presence of cardiovascular disease where straining must be avoided, one rounded teaspoonful of Perdiem™ taken once or twice daily will provide regular bowel habits. Take with a full glass of water or beverage.

FOR CHILDREN: From age 7—11 years, give one rounded teaspoonful one to two times daily. From age 12 and older, give adult dosage.

NOTE: It is extremely important that Perdiem™ should be taken with a plentiful supply of liquid.

HOW SUPPLIED: Granules: 100 gram (3.5 oz) and 250 gram (8.8 oz) containers.



ASOCIACION MEDICA DE PUERTO RICO

SEPRE ESTA FECHA: NOV. 25 - 29, 1980

ASAMBLEA ANUAL

CENTRO DE CONVENCIONES



WILLIAM H. RORER, INC.
Fort Washington, PA 19034

LYMPHOCYTIC TRANSFORMATION IN THE DIAGNOSIS OF CONGENITAL TOXOPLASMOSIS

Wilson, C. B., Desmonts, G., Courmeur, J., Remington, J. S.: *The New England Journal of Medicine*, Vol. 303: 785-788, 1980.

Aproximadamente 3,300 infantes nacidos cada año en los Estados Unidos son víctimas de infección congénita por *Toxoplasma gondii*. La mayoría de estos niños cursan de forma asintomática durante el período neonatal, pero eventualmente, muchos desarrollan secuelas importantes. Estas pueden reducirse con un tratamiento adecuado durante el primer año de vida. Sin embargo el diagnóstico de la enfermedad durante ese primer año ofrece algunas limitaciones, como por ejemplo: 1) La falta de sensibilidad de la prueba de anticuerpos IgM contra toxoplasma en el suero del infante. 2) La falta de disponibilidad en muchos centros hospitalarios del método de aislamiento del toxoplasma a partir de placenta o sangre del infante. 3) La poca eficacia diagnóstica de la prueba que detecta anticuerpos IgM anti-toxoplasma en el suero del infante durante el primer año de vida. La transformación linfocítica ante el antígeno de toxoplasma ha demostrado ser un indicador específico de infecciones previas en el adulto. En este estudio prospectivo se evalúa la transformación linfocítica ante el antígeno de toxoplasma en 25 infantes (edades entre 0.75 y 12 meses) con sospecha de infección congénita, utilizando un grupo control de 9 infantes. Se consideró el índice de estimulación positivo como indicativo de infección por toxoplasma aunque ésta, no se descarta por la negatividad de este índice. Se demuestra en el estudio que la positividad del índice de estimulación ante el antígeno de toxoplasma es un indicador sensitivo (84 por ciento) y específico (100 por ciento) de toxoplasmosis congénita y que esta sensibilidad es similar en pacientes asintomáticos (88 por ciento).

Como método diagnóstico, esta prueba compara favorablemente con el método de aislamiento del protozoo y es superior en sensibilidad a la prueba de detección de anticuerpos IgM. La sangre obtenida para la prueba puede ser conservada por ocho horas a temperatura ambiente sin que se altere el resultado de la misma, lo que permite su envío a centros que puedan procesarla. De acuerdo a este estudio se concluye que la transformación linfocítica ante el antígeno de toxoplasma es un método confiable al alcance de muchos centros hospitalarios para el diagnóstico de toxoplasmosis congénita durante el primer año de vida.

(Sometido por Rafael A. Quiñones Soto, MD)

TOXIC - SHOCK SYNDROME (TSS) - U. S.

Chesney, J., Chesney, R. W., Purdyn, W., et al - *MMWR* 29: 229, 1980

FOLLOW UP ON TSS - US

Daiser, J. P., Johns, R. E. - *MMWR* 29: 297, 1980.

Since its initial description in 1978, 131 cases of TSS have been reported to the Center for Disease Control, which has made this disease voluntarily reportable and is currently undertaking a nationwide study along with the Food and Drug Administration. The syndrome is characterized by the sudden onset of high fever, vomiting and profuse watery, diarrhea, occasionally accompanied by sore throat, headache, myalgias and "strawberry tongue". The condition progresses rapidly to hypotension and shock within 48 hours, accompanied by a diffuse, macular erythematous (sunburn-like) rash and non-purulent conjunctivitis. The patient may become disoriented or aggressive, and adult

respiratory distress syndrome, cardiac dysfunction and oliguric renal failure may develop. Laboratories reveal axothenia and increased serum creatinine, hyperbilirubinemia, increased creatinine Phosphokinase and leukocytosis with prominent shift to the left. Thrombocytopenia may be detected during the first week of illness, but during the second week thrombocytosis is seen. The case fatality ratio is 10.15 percent, otherwise the illness is usually resolved by the second week after onset, with desquamation of the rash, especially on the palms and soles.

The Wisconsin Health Department, which has been actively searching for and studying this condition, calculated an incidence of 3/100,000 menstruating women/year; incidence was higher in females less than 30 years of age. Ninety-six percent of cases reported to the Center for Disease Control were mostly young females and in 95 percent the onset of disease occurred during menses. Epidemiological surveys indicated an association with the use of tampons, especially continuous use during menses. There is a high incidence of cultivating *Staphylococcus aureus* from the vagina in these patients, and in those treated with penicillinase resistant penicillin recurrences were less frequent than in those not treated with these antibiotics. Since the organism has never been cultured from blood in these patients, it is postulated that a mutant organism is producing a highly active toxin which is responsible for this syndrome. The disease has also been reported in males, children and non-menstruating women, indicating that menstruation is not an absolute pathogenetic factor.

The differential diagnosis includes Kawasaki's disease, leptospirosis, rocky mountain spotted fever, viral exanthems and streptococcal scarlet fever. Treatment consists of vigorous fluid replacement and early recognition and many management of complications. Present Center for Disease Control recommendations include avoidance of use of tampons, or at least intermittent use, for several menstrual periods following an episode of TSS, particularly until eradication from the vagina of *S. aureus* if this organism is present. Also the use of a penicillinase resistant antibiotic may prevent recurrences in this disease.

Better characterization of the clinical manifestations of disease, more epidemiological data and investigation of causative factors are needed in order to

provide optimal management and control of the TSS.

(Submitted by Paul T. Harrington, MD)

CLINICOPATHOLOGIC FEATURES OF THE SYNDROME OF PRIMARY SCLEROSING CHOLANGITIS

Wiesner, R. H., La Russo, N. F. *Gastroenterology* 79: 200-206, 1980

La enfermedad llamada colangitis esclerosante primaria (CEP) se caracteriza por una inflamación y fibrosis de los ductos biliares extra-hepáticos con o sin envolvimiento de los ductos biliares intra-hepáticos. La enfermedad progresa lentamente hasta producir cirrosis hipertensión portal y finalmente fallo hepático. Estos autores repasaron los historiales de 265 pacientes con colangitis que fueron vistos en la Clínica Mayo de 1970 a 1977. Coledocolitiasis, estrecheces postoperatorias o colangiocarcinoma fueron las causas de colangitis en 215 pacientes. 50 pacientes cumplían con los criterios para el diagnóstico de CEP (estrechez difusa y/o irregularidad de los ductos biliares extrahepáticos diagnosticado radiológicamente o quirúrgicamente). Algunos de los hallazgos son los siguientes: 1) ocurrió más frecuentemente entre los 20 y 50 años (76 por ciento); 2) el 70 por ciento eran varones; 3) en el examen inicial 90 por ciento estaban sintomáticos (ictericia 68 por ciento, prurito 62 por ciento, dolor abdominal inespecífico (50 por ciento); 4) hepatomegalia en 28 por ciento y splenomegalia en 29 por ciento en el examen inicial; 5) 54 por ciento tenían enfermedad inflamatoria intestinal; 6) 81 por ciento tenían envolvimiento de los ductos extrahepáticos e intrahepáticos; solamente en 19 por ciento el envolvimiento era únicamente extrahepático; 7) un 33 por ciento murieron durante el seguimiento (intervalo de 5 a 108 meses, promedio de 57 meses); 8) la causa más común de muerte fue fallo hepático. Muchos de los pacientes recibieron terapia con esteroides y se

pensó que no fue beneficiosa.

(Sometido por Angel Olazábal, MD)

PURINOGENIC IMMUNODEFICIENCY DISEASES: CLINICAL FEATURES AND MOLECULAR MECHANISMS

Beverly S. Mitchell, MD, and William N. Kelley, MD; *Ann Arbor, Michigan - Annals of Int. Medicine, June 1980.*

Deficiencies of two enzymes that catalyze sequential reactions in the purine catabolic pathway have been causally associated with immunodeficiency states. Adenosine deaminase (ADA) deficiency results in severe combined immunodeficiency disease, while purine nucleoside phosphorylase (PNP) deficiency

results in an isolated T-cell defect. Recent work in this area has provided major new insights into the molecular pathology of these syndromes. Deoxyadenosine and deoxyguanosine, substrates that accumulate in ADA and PNP deficiency, respectively, appear to be selectively phosphorylated by lymphoid cells to the corresponding deoxynucleoside triphosphate, resulting in inhibition of DNA synthesis in these cells. Both deoxynucleosides are far more toxic to cultured T lymphoblasts than to B lymphoblasts. Adenosine and deoxyadenosine may have additional lymphotoxic effects mediated by inhibition of essential methylation reactions. These observations help to explain the immunologic manifestations of ADA and PNP deficiency. Perhaps more important, they lay the foundation for the use of deoxynucleoside or enzyme inhibitors, or both, as selective immunosuppressive and chemotherapeutic agents.

(Submitted by Edwin Mejías, MD, VAH)

MEDI QUIZ-INFECTIOUS DISEASE

CONTESTACIONES

1. C
2. C
3. C
4. B
5. C
6. B
7. C
8. A
9. A
10. C

CARTA AL EDITOR

August 5, 1980

Dear Editor:

The world's two major family practice groups will stage the first joint international educational forum in family medicine October 6-9 at the Rivergate Exhibition Center in New Orleans.

The joint meeting will be composed of the American Academy of Family Physicians' (AAFP) Annual Scientific Assembly and the Ninth World Conference on Family Medicine of WONCA, the World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians.

More than 7,000 family physicians from 40 countries are expected to participate in the variety of continuing medical education elements including scientific lectures by internationally renowned speakers, seminars and live teaching demonstrations. Each event is designed to help keep family physicians abreast of medical advances.

The AAFP, the largest medical specialty organization in the country, and WONCA have a great impact on medicine today. These

two groups will combine their efforts to provide a wide selection of unique medical activities that may well contain news of value to your readers.

May I take this opportunity to invite you to cover this unprecedented meeting. We will have a trained press staff available to help you get the information you need on any aspect of the AAFP Annual Scientific Assembly and WONCA Ninth World Conference on Family Medicine.

The scientific program will begin at the Rivergate on Monday, October 6, immediately following the close of the annual meeting of the AAFP's Congress of Delegates. The Congress will meet October 4-6 at the New Orleans Hilton.

A letter from the AAFP Scientific Program Chairman is enclosed. I hope to have the opportunity to meet with you at the New Orleans meeting.

Sincerely,

(SGD)

John S. Derryberry, MD
President
American Academy of Family Physicians

TRABAJOS PRESENTADOS EN LA REUNION ANUAL — AMERICAN COLLEGE OF PHYSICIANS OCTUBRE 1980

GATED BLOOD POOL IMAGING IN THE EVALUATION OF LEFT VENTRICULAR FUNCTION

Julio V. Rivera, FACP, Edgardo Hernández, MD, Mark A. Ficek, MSC - Veterans Administration Medical and Regional Office Center, San Juan, Puerto Rico.

The purpose of this study was to review and evaluate our initial experience in the study of left ventricular function (LVF) by blood pool imaging (99m Tc-RBC). Multiple gated images (MUGA) (20-30/cardiac cycle) were acquired in 50 patients at rest in a scintillation camera and dedicated computer. Ejection fraction (EF) and segmental ventricular wall motion were observed in each. Twenty two of these patients underwent contrast ventriculography. The reproducibility of the radionuclear method was studied by repeated imaging and that of contrast angiography by duplicate calculation by 2 independent observers. Correlation of EF between the 2 methods was good ($r=0.82$). Segmental hypokinesis or akinesis was detected in 23 patients; dyskinesis or aneurysm in 5. MUGA has been found to be a safe, convenient and reproducible method for the assessment of LVF.

MISONIDAZOLE AS A RADIOSENSITIZER

Arturo Ydrach, MD, FACP, Víctor A. Marcial, MD - University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

The background of radiobiology and develop-

ment of radiosensitizers will be reviewed, and the experience with misonidazole at the University of P. R. School of Medicine in protocols of the R.T.O.G. (Radiation Therapy Oncology Group) will be presented.

We are participating in four Phase III protocols of the R. T. O. G. comparing conventional radiotherapy with radiosensitized radiotherapy using misonidazole.

The experience with Phase II protocol No. 78-32 evaluating misonidazole combined with radiation in the treatment of locally advanced squamous cell carcinoma of the esophagus will be presented in detail.

At this time, there are 19 patients entered into this non-randomized study, evaluating toxicity to misonidazole and tumor response. The patient population, objectives, materials and methods, toxicity and tumor response will be presented. The future of radiosensitizers will also be discussed.

Hypoxic cells are present in human tumors. These hypoxic cells are radioresistant, and present a problem to local control with conventional radiotherapy. Among the areas of investigation being studied to enhance the radiobiologic effect of conventional radiation are the electron affinic drugs such as misonidazole.

RECOGNITION OF NOSOCOMIAL INFECTIONS BY PHYSICIANS IN-TRAINING

Ramón H. Bermúdez, FACP, Marlene Rivera, RN, Carlos H. Ramírez Ronda, FACP, and Luz E. Colón, VAH and UPR School of Medicine, San Juan, Puerto Rico.

During a six month period 275 episodes of nosocomial infections (NI) were reported by the Infection Control Practitioner (ICP) in a separate file.

Physicians-in-training (PIT) were requested to record NI in the physician's discharge note (PDN). Correlation between NI reported by ICP and recognized by PIT in PDN was 35 percent. PIT did not recognize NI in 33 percent of episodes and failed completing PDN in 32 percent of episodes of NI. Hospital summaries (HOS) were correlated with recognition and recording of NI by PIT. 80 percent of recognized NI were recorded in HOS. Most frequently recognized by PIT were wound and urinary infections. PIT in medicine recognized 43 percent of NI in PDN while in surgery PIT recognized 35 percent of NI. PIT at postgraduate level I (interns) recognized 18 percent of NI while at higher levels of training recognized 19 percent. NI were recorded more frequently in HOS (54 percent) than recognized in PDN by PIT (35 percent). Level of training did not correlate with recognition of NI. ICP should report NI in progress notes rather than PIT in physician's discharge note or hospital summaries.

ATYPICAL MYCOBACTERIA: 9 YEAR EXPERIENCE AT THE SAN JUAN VA HOSPITAL

Orlando L. Vázquez Torres, MD, (Member)*, Arturo R. Córdova, MD (Member), and María Medina, MS, MT, San Juan VA Hospital, San Juan, P. R.

Some authors have reported that with the advent of effective tuberculosis control measures, the relative frequency of isolation of atypical mycobacteria (A.M.) is increasing. This study was conducted to determine if a similar trend could be detected at the San Juan VA Hospital, to find out the frequency with which these organisms cause disease and to define its clinical presentation. All positive mycobacterial cultures from 1971 to 1979 were analyzed. Medical records of patients in which A.M. were isolated were reviewed and patients with disease due to these organisms were identified using standard criteria. Of a total of 1111 mycobacterial isolates, 174 (16 percent) were A.M. The mean relative frequency of A.M. isolates per year was

14.89 percent ± 2.82 (SEM), this did not show any significant trend for the study period. 27 patients met the criteria for disease caused by atypical mycobacteria. The organisms were isolated from sputum, lymph nodes, lung, skin, joint fluid, pleura and ascitic fluid. It is concluded that in this series the relative frequency of isolates of atypical mycobacteria has remained unchanged over the past 9 years, that disease caused by these organisms accounts for approximately 5 percent of all mycobacterial infections and that multiple sites can be affected.

*Recipient American Lung Association Training Grant.

COMPARATIVE ACTIVITY OF MOXALACTAM (MX), CEFOTAXIME (CX), MEZLOCILLIN (MZ) AND PIPERACILLIN (PP) AGAINST 194 BACTEREMIC STRAINS

S. Saavedra, PhD, MD, M. Nevárez, BSMT, A. Cruz, R. Cuevas, and C. H. Ramírez-Ronda, FACP. VA Med&ROC and UPR School of Medicine, San Juan, Puerto Rico.

MX, CX, MZ and PP are four new betalactam antibiotics. Their activity was compared in vitro among themselves and with that of cefazolin (CF), cefoxitin (CFX), cefamandole (CM) and carbenicillin (CB), against 194 bacteremic strains recovered in 1979. Studied were 25 each of *E. coli* (EC), *K. pneumoniae* (KP), *P. aeruginosa* (PA), *S. aureus* (SA), *S. epidermidis* (SE), *Enterobacter* (EB), *Serratia* (SR) and *Proteus* (PR). The MIC's were determined using the microdilution method with a Dynatech MIC-2000 in MH broth. MX and CX were equally active and the most active agents, with 90 percent of the strains of EC, KP, EB, PR and SR susceptible to 0.125 $\mu\text{g/ml}$ or less. MX and CX were more active than any of the 3 cephalosporins (CPS) tested. CX was more active than MX against PA (MIC₉₀ 32VS16). MX and CX were less active against SA and SE, MX was the least active. PP was the most active agent for PA, more active than MZ and equal in activity with MZ against EC, KP, EB and SR. 50 percent of the KP strains were susceptible to 200 $\mu\text{g/ml}$ or less of MZ or PP. MZ

and PP are more active than CB. MZ and PP activity against SA and SE is similar. The in vitro activity of MZ and CX is superior to any of the agents tested against GNB, except PA in which PP is the most active agent. MZ and PP were more active than CB against all GNB tested.

ORAL OXAMNIQUINE FOR THE TREATMENT OF CHRONIC SCHISTOSOMA MANSONI INFECTION IN PUERTO RICO.

G. Vázquez, (Associate), M. Fiorilli, MD, E. Ruiz-Tiben, Z. Sotomayor, MD, and C. H. Ramírez Ronda, FACP. - UPR School of Medicine, San Juan Laboratories and VA Med&ROC, San Juan, Puerto Rico.

To evaluate the efficacy and safety of oral oxamniquine we conducted a double-blind crossover study of 31 male patients between the ages of 17 and 38 who were excreting an average of 100 or more *Schistosoma mansoni* eggs per gram of feces (EPG). Serological tests results (complement fixation, indirect immunofluorescence and circumoval precipitating tests) eosinophil counts and *S. mansoni* egg counts (modified Ritchie technique) remained essentially unchanged among 15 patients before and three months after receiving placebo. No spontaneous cures occurred in the placebo group. The placebo treated group and 16 other subjects were given oxamniquine at a dose of 12-15 mg/kg of body weight. Twenty of 31 oxamniquine treated patients were no longer passing eggs on day 30 post treatment. After a six month follow-up the pretreatment geometric mean egg count was reduced by more than 99 percent (from 230.0 EPG to 1.3 EPG). Absolute eosinophil counts increased from an average of 449 before treatment to an average of 2,271 at one month post treatment - a fivefold increase. The most common side effects observed were: urine discoloration, 42 percent; dizziness, 39 percent; and abdominal discomfort, 30 percent. These side effects were mild and self-limited. These results showed that, at a dose of 12-15 mg/kg, oxamniquine was both a well-tolerated and highly effective treatment for chronic *S. mansoni* infection in this population.

EFFECT OF PROSTAGLANDIN (PG) INHIBITION ON DEOXYCOLIC ACID (DOC) INDUCED PANCREATITIS (P) IN THE RAT

Angel Olazabal, FACP and Luiz Nascimento, MD - Medical and Research Services, VA Hospital; Dept. of Medicine, University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

The effects of pretreatment with indomethacin (IN) and of a fat free diet (FFD) for one week on the outcome of DOC-induced P were individually evaluated. P was induced by injection of 0.2 or 0.3 ml of 3 percent DOC solution into the pancreatic duct. The mortality rates at 24 hours for these groups were 11 and 56 percent respectively. Pretreatment with IN 30-60 min prior to induction of P increased the mortality rate in the 0.2ml group to 56 percent ($p < 0.05$) and in the 0.3 ml group to 89 percent ($p = NS$). Similar or larger volumes of 0.9 percent saline injected into the pancreatic duct failed to produce P as measured by serum amylase (SA) and histologic findings. Pretreatment with IN in saline injected rats did not alter SA, histology or mortality rate. Animals fed a FFD and injected with DOC had a mortality rate similar to DOC + IN group. Intraductal injection of saline to rats fed FFD failed to induced P. In conclusion our data show that: 1. the mortality rate of DOC-induced P in the rat is related to the dose injected; 2. similar or larger volumes of 0.9 percent saline into the pancreatic duct fail to produce P; 3. pretreatment with IN or FFD worsen the mortality rate in the DOC-induced P but have no effect in the saline injected rats. These results indicate that under the experimental conditions reported an intact PG system is of utmost importance in the prognosis of pancreatitis.

PURULENT PERICARDITIS

Twenty nine cases of Purulent Pericarditis from the Children's Hospital of Santo Domingo, during the last 5 and a half years are reviewed. The diag-

nosis was established by clinical data, X-Ray and Electrocardiographic Findings, Pericardiocentesis and culture of Pericardial fluid.. There was not any sex preference. Most of the cases ranged between 6 and 10 years. A pneumonia as main infective cause was found in 51.7 percent.

Staphylococcus coagulase positive was found in 76.9 percent. The most important clinical findings were: fever, 100 percent, difficulty in breathing, 96.5 percent, hepatomegaly 89.6 percent, diminished heart sounds, 68.9 percent, chest pain, 41.3 percent and pericardial friction rub, 41.3 percent.

There were 5 casualties.

MINOXIDIL IN THE TREATMENT OF REFRACTORY MALIGNANT HYPERTENSION

Salomon Jorge, MD - Universidad Católica Madre y Maestra School of Medicine, Santiago, Dominican Republic.

Five patients with malignant hypertension resistant to conventional drugs including sodium nitroprusside have been treated with the still investigational agent minoxidil, a potent direct vasodilator. Four of the 5 cases were of renal hypertension, the remaining one, of uncertain etiology. Three were on maintenance hemodialysis, one of them on the way to the operating room to undergo bilateral nephrectomy.

All were males and the age ranged between 16 and 54 years. Follow-up extended from one week to seven months and the dosage varied from 5 to 40 mg in divided doses or in a once a day dosage. Consistent, remarkable control of the blood pressure was obtained in all cases. In one instance the blood pressure dropped from 300/190 to 160/60 in a matter of hours; concomitantly the optic fundoscopic findings responded favorably, regressing from class IV to class III, II or even to class I in one case. In order to control sodium retention and reflex tachycardia, diuretics and beta-blockers were associated to minoxidil. Patient acceptance of the drug was excellent in the five cases.

The side effects were limited to mild hyper-

trichosis in one patient and transient ankle edema in another one. No patient experienced postural orthostatic hypotension.

FATE OF PATIENTS WITH COMPLETE LEFT BUNDLE BRANCH BLOCK (CLBBB)

Francisco Jaume, (Member) Fernando Torres, MD and Luis Acevedo Lazarini, MD, Mayaguez Medical Center, Mayaguez, Puerto Rico.

The fate of forty two patients admitted to the hospital with CLBBB have been followed over a period of 8 years. Twelve of the records could not be analyzed because of incompleting medical information. The remaining medical records of 19 males and 11 females are the subject of this report. At the time of entry in the study, the average age of the males was 69.7 years and the females 61.3 years and 7/30 (23 percent) were free of heart disease.

Only six out of 30 patients were alive at the end of eight years. Sixteen of 30 patients (53 percent) were dead at the end of two years.

Patients alive at the end of two years (Group A) were compared with those who had died (Group B).

There was no significant difference in the prevalence and type of heart disease between the two groups. The patients who died within two years were older (average age 70 years), sixty five percent of them had enlarged hearts (cardio-thoracic ratio greater than 55 percent), and sixty one percent had left axis deviation greater than 30 degree.

It is concluded that patients with clinical evidence of heart disease admitted to a general hospital with CLBBB have 50 percent chances of being dead within two years.

CARDIAC ISOENZYMES PROFILE AND NON-DIAGNOSTIC ELECTROCARDIOGRAM

V. M. Toledo MD (Associated) F. M. Cortés, MD, FACP, J. Morales, MD, Damas Hospital, Ponce, Puerto Rico.

From the review of 207 cases admitted to Damas Hospital due to chest pain and/or Congestive Heart Failure with the suspected diagnosis of Acute Myocardial Infarction (AMI); we found a small group of 46 patients (pts.) in which the Electrocardiogram (E.K.G.) did not help in the definitive diagnosis of AMI. Three subgroups were classified:

Group I: A total of 22 cases in whom the EKG presented with: a) symmetrically inverted T waves (ischemic); b) 1 MM. St segment depression for 0.08 sec.; c) combination of both patterns (a and b); and the so called non specific ST-T changes. In 7 pts. the Cardiac Isoenzymes Profile (CIP) was abnormally elevated indicative of myocardial necrosis. In the other 15 pts. the normal CIP values ruled out myocardial necrosis.

Group II: 17 pts. presented with complete left bundle branch block. In one pt. the EKG was considered diagnostic of AMI while CIP confirmed the diagnosis in 11 pts. (64.7 percent); in the remaining 5 pts. the diagnosis could not be confirmed.

Group III: 7 pts. presented with complete right bundle branch block. In 4 of 7 the ST-T changes were suspicious of AMI while in 5 of 7 CIP confirmed the diagnosis of AMI; while in 2 pts. with normal CIP the AMI could not be confirmed.

Conclusion: In pts. suspected of AMI and with non diagnostic EKG the determination of CIP will confirm diagnosis in large percentage of patients.

CLASSIFICATION AND RESULTS OF 184 PATIENTS STUDIED FOR "HYPOGLYCEMIA" BASED ON 5 HR ORAL GLUCOSE TOLERANCE (OGTT) TESTS.

Francisco Aguiló, Jr., MD, FACP, Vilma Rabell, MD, Myriam Allende, MD (Assoc.) and R. Ortiz-Carrasquillo, MD (Tech.

assist. of María C. Vázquez, MT, Cucha Suárez, BS & Nilda Ramos MT) Dept. of Medicine, University of P. R. School of Medicine, San Juan, Puerto Rico.

In the past 10 years, over 250 patients have had evaluation for "hypoglycemia". An analysis of 184 with 5 hr OGTT (100 Gm dose) revealed a 2:1 preponderance of females (F) to males (M). Mean age was higher for M than F: 35.4 ± 17.4 vs. 30.9 ± 11.3 , $p < 0.05$.

At our lab. relation between whole blood (x) & plasma glucose (y) is given by: $y = 1.03x + 4.6$ mg/dL; the over-all mean fasting glucose (85.8 ± 14.25 SD) minus 3SD gave a cut-off value of 43 mg/dL for x, corresponding to 46.9 mg/dL for y (mean value: 45 mg per dL). With such cut-off point, only 17 (9.1 percent) of patients really had hypoglycemia; 108 patients (58 percent) had "normal" values (over 60 mg/dL), while 61 (33 percent) remained as an ill-defined group.

Concomittant plasma immunoreactive insulin (IRI) was higher at 3 hrs in F than M, yielding higher insulin/glucose ratio: 0.86 F vs. 0.45 M, probably related to Higher body weights. Five patients were probably diabetic. Symptoms among the "normal" group did not correlate well with BG & were frequently due to hyperventilation.

Among the hypoglycemic group, there was 1 insulinoma, 1 partial gastrectomy, 1 pheochromocytoma and a still unresolved hypoglycemia in a pregnant "juvenile" diabetic while off exogenous insulin.

"Non-hypoglycemia" is therefore the prevalent diagnosis in this group of patients.

A LONGITUDINAL PROSPECTIVE STUDY OF CHRONIC COMPLICATIONS IN PUERTO RICAN DIABETIC PATIENTS

Francisco Aguiló, Jr., MD, FACP, Myriam Allende, MD, Associate and Pablo I. Altieri, MD, University of P. R. School of Medicine, San Juan, P. R.

Thirty four non-insulin dependent diabetic

patients were prospectively followed up for a total ave. period of 14 years, ending in 1978. Among this group we assessed the prevalence of coronary artery disease (CAD), and looked into a possible correlation with degree of blood glucose (BG) control and other known coronary risk factors. The prevalence of silent myocardial infarction (MI) was investigated clinically and through comparison of baseline and 1978 ECGs and VCGs. Presence of other chronic complications of diabetes was also studied.

Twenty one patients (62 percent), had clinical and/or ECG-VCG abnormalities compatible with CAD. In 16/21 (76 percent), abnormal ECGs and VCGs remained unchanged; 5/21 (24 percent) had initially normal ECGs-VCGs. Only one instance of silent MI was encountered and showed both by ECG and VCG. Next most frequent complications were cataracts 9/34, (26 percent) and background retinopathy (6/34, 18 percent).

Thirteen patients (38 percent) had no demonstrable complication. As compared with the complicated group, these had statistically significant lower mean age (57 ± 6 vs. 66 ± 8 yrs. $p < 0.01$), and lower baseline BG (118 ± 32 vs. 147 ± 33 mg/dL, $p < 0.05$). No statistically significant difference were found intergroup as to sex, serum cholesterol, triglycerides or relative body weight. Smoking and hypertension were oddly, negatively correlated with such complications.

PULMONARY FUNCTION IN HEMODIALYSIS PATIENTS

Raúl J. Moreno, MD, Arturo R. Córdova, MD, (Member), Rafael Ramírez González, MD and Eduardo Santiago Delpín, MD, San Juan VA Hospital, San Juan, P. R.*

Conflicting results have been published with regards to the effect of chronic hemodialysis (H.D.) on pulmonary function. This study was undertaken to determine if an association exists between pulmonary function abnormalities and length of dialytic therapy. H. D. patients being considered for renal transplantation were routinely referred for pulmona-

ry function tests. Those with a negative history of smoking or previous lung disease were entered in the study. Twenty five patients met the admission criteria. They were divided in two groups. Those with less than 24 months on H. D. (16 patients) Group I and those with more than 24 months on H. D. (9 patients), Group II, FEV₁, VC, FEV₁/VC, RV, TLC and RV/TLC expressed as percent predicted for the patients age, height and sex were compared for the two groups with the following results:

	FEV ₁	V.C.	FEV ₁ /VC
Group I	89.9 (± 3.6)	90.9 (± 3.6)	82.3 (± 1.8)
Group II	73.6 (± 4.2)	72.3 (± 4.2)	79.7 (± 2.4)
P-Value	.01	.01	N. S.
	RV	TLC	RV/TLC
Group I	110.2 (± 8.6)	96.5 (± 3.3)	30.6 (± 1.8)
Group II	132.8 (± 10.1)	93.4 (± 5.9)	43.1 (± 1.9)
P-Value	N. S.	N. S.	.001

(Results expressed as mean \pm S. E. M.)

This data supports that hyperinflation and a restrictive ventilatory pattern develop in patients with more than 24 months on H. D. compared with those with a shorter duration of therapy. The mechanisms responsible for these findings are not known.

*-Recipient Summer Scholarship P. R. Lung Association.

FIBEROPTIC BRONCHOSCOPY: EXPERIENCE AT THE SAN JUAN VA HOSPITAL

Salvador Abreu, MD, (Associate), Arturo R. Córdova, MD (Member, Orlando L. Vázquez Torres, MD (Member)*, and Rubén Rodríguez, MD, San Juan VA Hospital, San Juan, P. R.

For the past two years Fiberoptic Bronchoscopies (FOB) have been used at the San Juan V. A. Hospital for the evaluation of thoracic lymphadenopathy, pulmonary parenchymal abnormalities and/or hemoptysis, 157 consecutive procedures done on 127 patients were prospectively analyzed to determine the usefulness and the rate of complications of this procedure and to compare these results with those in the literature. FOB was successful in diagnosing 57 of 82 cases (70 percent) in which a specific final diagnosis could be made. In the group, FOB correctly identified 62 percent of primary lung cancers, 86 percent of pulmonary infections, 83 percent of patients with interstitial lung disease and 100 percent of patients with atelectasis. There were 45 patients in which no specific diagnosis could be made by all available means; FOB revealed non-specific tracheobronchial abnormalities in 32 (71 percent) and was normal in 13 (29 percent). On follow up, 37 patients are doing well and 8 are lost to follow-up. During FOB, two patients developed bronchospasm, 2 pneumothorax and 1 bradycardia, for a complication rate of 3 percent. These results show that FOB is a safe and effective diagnostic method for patients with pulmonary disease. The present experience is similar to that reported in other centers.

*Recipient American Lung Association Training Grant.

LIVER SCINTIGRAPHY: A PREDICTOR OF DISEASE SEVERITY IN VISCERAL MANSONI SCHISTOSOMIASIS.

S. Sostre, F. Silva, M. K. Zaidi. University of Puerto Rico, San Juan, Puerto Rico.

We have classified the liver scans of patients

with chronic schistosomiasis into five groups of increase involvement severity. Mild visceral involvement is associated with a slightly enlarged spleen. With heavier disease, the right hepatic lobe decreases in size, the left lobe enlarged and the spleen grows further. In severe cases, the left hepatic lobe finally "shrinks" and the spleen becomes hot and enormous. Bone marrow uptake is rare even in advanced cases, but focal hepatic defects, probably caused by conglomeration of fibrous tissue, may be seen in up to 20 percent of these patients.

In this study the scintigraphic classification of 20 patients with proven schistosomiasis was correlated with the clinical findings to determine if the proposed classification has clinical usefulness. None of the seven patients in groups I and II had symptoms of signs of portal hypertension. However, 10 of 11 patients in groups IV and V developed esophageal varices and 9 had episodes of hematemesis. One of 2 patients in group II had varices but no bleeding.

These findings suggest that proposed scintigraphic classification provides an accurate index of hepatosplenic involvement severity in patients with chronic schistosomiasis. In addition the liver scan has been a good tool to detect early hepatic involvement demonstrating a higher sensitivity than liver function tests.

GALLIUM (^{67}Ga) LOCALIZATION IN INTRATHORACIC STRUCTURES

Julio V. Rivera, FACP, Arturo Córdova, (Member), José R. Fernández, MD, Eduardo Ferriol, BS - Veterans Administration Medical and Regional Office Center, San Juan, Puerto Rico.

Among 154 patients who underwent whole body scan (^{67}Ga) during an 8 months period 64 (43 percent) showed abnormal localization at intrathoracic structures. This included the following causes: primary carcinoma of the lung, 27; lymphoma, 8; pulmonary fibrosis, 5; metastatic carcinoma, 4; pleurisy, 4; tuberculosis, 3; pneumonia, 2; sarcoidosis, 1; *Pneumocystis carinii* pneumonia, 1; undetermined cause, 9.

Comparison to radiologic examination revealed

a similar distribution of abnormality in 26 patients; in 22 gallium the scan indicated more extensive or undetected disease, while the opposite was true in 4 patients. More extensive disease on gallium scanning was most often seen in lymphoma (6/8) and carcinoma of the lung (6/27).

It is concluded that gallium scanning of the intrathoracic structures is useful as a supplementary examination in the evaluation of several diseases. In some cases, as in pulmonary fibrosis, the gallium scan was helpful in the decisions of patient management.

COMBINED EXERCISE EKG AND 201 THALLIUM SCINTIGRAPHY IN THE DIAGNOSIS OF CORONARY ARTERY DISEASE

J. A. Morales, MD (Member), F. Cortés, MD FACP, and C. Pimentel, MD, Damas Hospital, Ponce, P. R.

50 pts. underwent stress ECG & Thallium imaging. Exercise was in a graded fashion (Bruce) up to a predicted maximal heart rate, onset of chest pain, ventricular arrhythmias or significant ST segment depression. 201 Thallium 1.5-2 mci was injected 30-60 secs. before end of exercise and imaging started 5-10 mins. later & repeated at 3-4 hrs. Scans were interpreted by one observer without knowledge of the ECG findings and were classified as pos. or neg. Positive studies were reclassified into pos. redistribution and no redistribution. ECG's were read as pos. (over 1 mm ST segment depression over 0.08 sec) neg. or non-diagnostic. 28 pts. were abnormal. 9 of these had pos ECG's, 13 neg. and 6 non-diagnostic. 6 pts. with pos. scans had coronary arteriography, 4 were pos. and 2 normal. 3 of the former had pos. ECG's and of the latter 1 had IHHS and the other was a false pos. study. 8 pts. showed significant redistribution, 2 had normal ECG's, 4 pos. and 2 non-diagnostic. 3 of these had coronary arteriography findings which correlated with the scan and underwent bypass surgery. This preliminary data show an increased sensitivity in the detection of CAD when combined with exercise ECG in a single and non invasive manner.

ACUTE FATAL HEMORRHAGIC PNEUMONITIS IN SYSTEMIC LUPUS

Braulio Quintero, MD, Russel Del Toro, MD, FACP, San Juan city Hospital, San Juan, P. R.

Five patients with well known S. L. E. according to A. R. A. criteria, developed an acute and fatal course whose main features were hemoptysis, pulmonary hemorrhage, respiratory insufficiency and death in a short period of time, usually two or three days. All were young females, most of them with active disease except one patient whose S. L. E. was not active serologically. Pulmonary involvement was not easily predicted, and was abrupt in onset. Multiple systemic complications arose. Diagnosis and therapy of main pulmonary injury was difficult in all cases due to the characteristically aggressive picture. Hemorrhagic pneumonitis is a fatal complication of the respiratory system and probably the most, in systemic lupus patients. Diagnosis and therapy should be early and aggressive. Conventional therapy with regular doses of steroids were not of help. High doses of steroids and probably Plasmapheresis are suggested.

SYSTEMIC LUPUS ERYTHEMATOSUS AND PREGNANCY

Esther N. González Parés, MD, FACP, David Martínez, MD (Member) and Agustín Rodríguez Pérez, MD - Rheumatic Diseases Section, School of Medicine, University of Puerto Rico, and MIC University Hospital, San Juan, P. R.

It has been said that pregnancy can be deleterious to patients with Systemic Lupus Erythematosus. Our aim was to determine the outcome of pregnancy and its effect on the disease in patients who had been diagnosed as SLE.

All the patients who became pregnant after the diagnosis of SLE was made were included in the study. 44 patients were included in the study. In 13 patients the diagnosis of the disease was made during

pregnancy. There were 73 pregnancies among the 44 patients. Of these, there were 49 completed pregnancies, 9 stillbirths, 12 spontaneous abortions and 1 therapeutic abortion. One patient developed an ectopic pregnancy and one patient died.

In the patients with active disease at conception, the disease remained active in 89 percent and became inactive in 11 percent. In patients with inactive disease at conception, the disease remained inactive in 76.9 percent and became active in 23.1 percent.

Corticosteroids were used by 69.86 percent of patients. One patient was in chlorambucil. 10.95 percent of children developed fetal abnormalities.

There are some patients with SLE who may attempt pregnancy, with favorable prognosis for both mother and child.

COMPARISON OF AGE RELATED HISTOLOGY IN MINIMAL CHANGE NEPHROTIC SYNDROME

L. E. Lergier-Dexter, (FACP), R. Galarza, MD, M. Molina, MD, J. M. Vázquez, MD. Depts. of Medicine & Pathology, VA Hospital & University of P. R. School of Medicine and Dept. of Pediatrics, San Juan City Hospital, P. R.

The age of onset of a disease process may be an important determinant of its course, since it affects the ability of the host to respond to injury. In order to evaluate the contribution of age to the histological appearance of minimal change (MC) nephropathy, we reviewed and compared the histopathology of 115 renal biopsies of patients with nephrotic syndrome and findings of minimal glomerular disease. For the purpose of analysis the patients were divided by age Group I: 1-20 yrs, n=14; 55 males, 57 females. Histological findings were categorized numerically according to severity and expressed as percentages. The lesions observed revealed a significant age related increase in the number of glomeruli with sclerosis in Gr III; (16 ± 4 percent) $p = 0.05$; as compared to Gr II; (7 ± 1 percent $p = 0.01$; and to Gr I: (7 ± 1 percent). Interstitial fibrosis increased with age: (Gr I: 12 \pm

3 percent; Gr II: 45 ± 12 percent; Gr III: 65 ± 15 percent. Atrophy of tubules was more prominent in the adults, (Gr II: 33 ± 1 percent; Gr III: 24 ± 2 percent) than in Gr I (6 ± 1 percent). Arteriolar and mesangial changes were equally distributed. EM findings of subendothelial sloughing of the basement membrane were common in all groups. This data suggests that patients with MC nephropathy have an age related increase in sclerosis of glomeruli and interstitial fibrosis. Atrophy of tubules was commonly observed in the adults; other changes were similar in all groups.

EXPERIENCE WITH CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD) OF SAN JUAN VAH

Tomás Rivera, RN, Laura E. Lesprier-Dexter, MD, FACP

CAPD has emerged as an excellent form of therapy for the treatment of end stage renal disease (ESRD) because of excellent clearance of middle molecules (uremic toxins), minimal dietary restrictions, improvement in clinical status, freedom from machines and economy. Selection of candidates, a trained staff and control of complications are important factors that determine the success of a newly established program.

A total of nine patients (pt.) have been successfully trained in our center during a four month period; three pt. were incorporated to our program after training. A group of 14 nurses have been trained and qualified for delivery of care and training of patients. Pt. were carefully selected in team approach; selection criteria; cooperative pt. willing and able to follow a technique. Etiology of renal disease were as follows: Chronic glomerulonephritis (6); tubulo-interstitial disease (2); diabetes mellitus (1); hypertension (2); multiple myeloma (1). Duration of programs: 53 pt./mo. (1-12 mo.) included off center trainees. Biochemical values show evidence of control with liberal diet, no fluid or sodium restrictions. Clearance obtained in 24 hrs: BUN: 1-11 gm; Na: 300-375 mEq;

K: 50-56 mEq; Fluid: 3000 \pm 280cc; Complications: Infectious: Cath site infections 1 (5 pt./mo.); peritonitis 1 (5.3 pt./mo.). Technical-surgical: leak (3) Cath failure (3); Dissection (1). Patients acceptance is excellent. Conclusion: CAPD has been effectively established in our institution with excellent control of renal insufficiency and patients' acceptance. Infections, although easily controlled, are still the most serious complications to be prevented.

CLINICO-EPIDEMIOLOGICAL FEATURES OF 102 CONSECUTIVE CASES OF ULCERATIVE COLITIS IN PUERTO RICO

Micames, Carlos, MD (Member), Zaiter, Juan, MD, University District Hospital, San Juan, Puerto Rico.

The experience at the Puerto Rico Medical Center in 102 cases with definite diagnosis of ulcerative colitis recorded from 1974 through 1980, of which 80 percent were followed-up, were reviewed. There were 59 women and 43 men having a mean of 7.8 years with the disease.

The incidence of ulcerative colitis was higher in whites, but the mean age of onset was younger in negros. Rectal bleeding, diarrhea and abdominal pain were major initial complaints. The diagnosis was usually made during the first year of the disease. The intermittent clinical course was the most frequently found. Eighty-four patients required hospitalization, and 22 of them had surgery, five on an emergency basis.

The most frequent systemic complications were anemia, arthralgia and chronic liver disease. The

local complications were: 8 colonic strictures, 7 perianal diseases, 3 toxic megacolons, and 2 inoperable carcinomas. Five patients died from causes related to colitis.

This study suggests that ulcerative colitis is not uncommon in Puerto Rico, that the sigmoidoscopic appearance could be confused with endemic entities such as schistosomiasis and tropical sprue, that the outlook of the disease in the tropics is similar to other geographical areas, and aggressive carcinoma continues being a prevalent undesirable complication considering the prevalence of this neoplasia in the Island.

ARE WE ORDERING UNNECESSARY AMYLASE STUDIES?

José M. Torres Gómez, FACP - Veterans Administration Hospital, San Juan, Puerto Rico.

The clinical indication for requesting serum amylase studies in 56 instances was analyzed using 8 pre-established criteria as guidelines. The request was not considered justified only when all criteria were absent from the clinical record. Under these conditions, the test was found to be justified in only 24 cases (43 percent). The results were normal in 45 cases (80 percent). Furthermore, the degree of abnormality in nine was not significant, thus only two results could be considered truly abnormal to support the possibility of acute pancreatitis. A plea is made for physicians to be more conscientious when ordering laboratory tests, serum amylase in particular, since it has a very low yield and adds significantly to the cost of medical care.

**LA PRUEBA DE ESFUERZO MODIFICADA TRES SEMANAS
DESPUES DE UN INFARTO NO COMPLICADO:
¿DEBE HACERSE? ¿POR QUE?**

(Pregunta sometida por el Dr. R. Palou, Guayama, P. R.)

Nuestra contestación a estas preguntas es en la afirmativa. Los propósitos que nos llevan a hacer esta prueba de esfuerzo (PE) en este grupo de pacientes son los siguientes: 1) Descubrir arritmias ventriculares latentes, 2) Descubrir isquemia miocárdica clínicamente importante, 3) Estimar capacidad funcional cardíaca, 4) Precisar con más exactitud el pronóstico.

¿Qué nivel de esfuerzo se debe utilizar y cuán tempranamente debe de efectuarse esta PE? Usualmente estos pacientes han sido sometidos a un nivel de esfuerzo submáximo (1-10), esto es, la PE es terminada al paciente alcanzar el 60-70 por ciento de la frecuencia cardíaca máxima de acuerdo a la edad (usualmente 120-130/minuto) o el trabajo equivalente a 4-5 METS, si el enfermo anteriormente no ha desarrollado síntomas tales como dolor anginoso, disnea, fatiga, arritmias ventriculares, hipotensión, mareos, etc. Es bueno señalar que al momento de conducir la PE el paciente tampoco debe tener evidencia de fallo cardíaco congestivo (la presencia de S_3 al descanso usualmente excluye la PE), dolor anginoso reciente, o evidencia de arritmias ventriculares pobremente controladas.

Antes de ser dado de alta el paciente, la PE se conduce bajo supervisión médica, usualmente entre 7-14 días después del infarto (6).

1) Descubrir arritmias ventriculares la-

tentes: Se asume que pacientes con arritmias ventriculares están sujetos a un riesgo mayor de muerte súbita. Basado en esto, Ericsson y colaboradores iniciaron tratamiento antiarrítmico en 11 de los 100 pacientes ejercitados.

2) Detectar isquemia miocárdica: Se ha documentado que en un por ciento significativo de pacientes ejercitados en un período temprano post-infarto, la depresión isquémica del segmento ST ($\downarrow \overline{ST}$) ocurre sin estar acompañada de dolor anginoso (4, 6, 7). Por lo tanto, mediante la PE podemos detectar isquemia miocárdica silenciosa, indicándonos que existen áreas de miocardio a riesgo de nuevos sucesos isquémicos. La detección de isquemia latente y arritmias ventriculares a niveles moderados de esfuerzo resultó en el cambio del manejo del 21 por ciento de los 62 pacientes ejercitados en la serie de Smith y colaboradores (5) y del 13 por ciento en la nuestra (7).

3) Utilidad en el pronóstico: Se sabe que el pronóstico a largo plazo, en pacientes con enfermedad coronaria, se halla en proporción directa al número de vasos afectados por esta enfermedad.

Turner y colaboradores (10) correlacionaron los resultados de la PE y la coronariografía dentro de las primeras 3 semanas después del infarto. Encontraron que una

PE positiva (dolor anginoso y/o $\downarrow \overline{ST} \geq 0.1$ mV) era específica (100 por ciento) para enfermedad coronaria en más de un vaso, pero una PE negativa correlacionó con enfermedad de solo un vaso en 50 por ciento de los casos (sensitividad baja).

Theroux y colaboradores (6) reportaron que la mortalidad a un año y la incidencia de muerte súbita eran ambas mayor de 10 veces en pacientes que tuvieron $\downarrow \overline{ST} \geq 0.1$ mV que para pacientes sin esta respuesta.

Recientemente, Davidson y DeBusk (9) concluyen que $\downarrow \overline{ST} \geq 0.2$ mV y el alcanzar esfuerzo máximo menor de 4 METS, tenían valor predictivo para episodios coronarios (infarto de miocardio, muerte súbita y detención cardíaca) en pacientes seguidos por 2 o más años. Angina de pecho inducida por la PE y $\downarrow \overline{ST} \geq 0.2$ mV fueron de valor predictivo en casos quirúrgicos (cirugía de puente aorto-coronario). No se ha reportado mortalidad ni re-infarto de miocardio como consecuencia de la PE.

Finalmente, creemos que el mayor beneficio obtenido como resultado de efectuar la PE antes de ser dado de alta el paciente, es el poder orientar al paciente con criterios objetivos en cuanto a las actividades físicas que puede hacer durante su convalecencia, lo cual parece ser también beneficioso, a la psiquis del paciente (3,5).

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New evidence is in: Treatment of mild hypertension can save lives

Even among patients with DBP in the low 90s, systematic therapy significantly reduced mortality:

- Of nearly 11,000 hypertensives identified by the Hypertension Detection and Follow-up Program, slightly more than 70% had mild hypertension (DBP 90-104 mm. Hg).¹
- Half were given systematic and aggressive care in HDFP centers; half were referred to customary sources of medical care.
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BRIEF SUMMARY

Indications: Hypertension; adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and

related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg (white, scored), 50 mg (aqua) in bottles of 100, 1000 and 5000, 25 mg (peach) in bottles of 100 and 1000, unit-dose blister packs, boxes of 100 (10 x 10 strips).

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In recurrent urinary tract infections



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The high degree of efficacy of Septra DS was confirmed in a study of 59 patients with recurrent pyelonephritis. All patients had upper urinary tract disease as evidenced by fever $\geq 100.4^{\circ}$ F and/or flank pain, and $\geq 10^5$ organisms/ml of urine. After two weeks' therapy and up to seven days post-therapy, Septra achieved bacteriologic cure ($\leq 10,000$ organisms/ml of urine) in 91.5% of patients.¹

And during the critical "recurrence" period from one to four weeks post-therapy, this excellent response rate was well maintained. Of the 53 patients evaluated at that time, 51 (96.2%) were still infection free.¹

Unlike many other antibacterials for the treatment of urinary tract infections, Septra DS is administered on a convenient b.i.d. dosage schedule.

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What makes Septra DS good for the tough areas—the kidneys—makes it good for the not-so-tough. Septra DS provides antibacterial action in the bladder, via urine and blood, against susceptible strains of major pathogens that cause recurrent cystitis.



And along the route to recurrence

During therapy, Septra DS diffuses into vaginal fluid² and into the bowel.^{3,4} By eliminating potential uropathogens from the fecal flora, and bathing the periurethral area in an "antibacterial" vaginal fluid, Septra DS helps block the most common route to reinfection in women.

Maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination during therapy. Septra is contraindicated in children under two months old.

Please see prescribing information on next page.



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Research Triangle Park
North Carolina 27709

Septra® DS B.I.D.

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole

Septra® Suspension B.I.D.

Each teaspoonful (5 ml) contains: 40 mg trimethoprim and 200 mg sulfamethoxazole

Septra® DS Tablets Double Strength

Septra® Tablets

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INDICATIONS AND USAGE:

URINARY TRACT INFECTIONS: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morgani*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

NOTE: Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of these urinary tract infections.

ACUTE OTITIS MEDIA For the treatment of acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in the judgment of the physician Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to *Haemophilus influenzae* resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.

SHIGELLOSIS: For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

PNEUMOCYSTIS CARINII PNEUMONITIS: For the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period. Infants less than two months of age.

WARNINGS: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A β -hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths associated with administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides.

Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBCs are recommended; therapy should be discontinued if a significant reduction in the count of any formed blood element is noted.

PRECAUTIONS: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6 phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Since Septra may prolong prothrombin time in patients on warfarin, coagulation time should be reassessed when Septra is given.

ADVERSE REACTIONS: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. **Blood Dyscrasias:** Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. **Allergic Reactions:** Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization,

arthralgia and allergic myocarditis. **Gastrointestinal Reactions:** Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. **C.N.S. Reactions:** Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. **Miscellaneous Reactions:** Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarthritis nodosa and L. E. phenomenon have occurred.

Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: The usual adult dosage for the treatment of urinary tract infections is two tablets or four teaspoonfuls (20 ml) every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose —every 12 hours	
lb	kg	Teaspoonfuls	Tablets
22	10	1 (5 ml)	1/2
44	20	2 (10 ml)	1
66	30	3 (15 ml)	1 1/2
88	40	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15-30	Half of the usual dosage regimen
Below 15	Use Not Recommended

PNEUMOCYSTIS CARINII PNEUMONITIS:

The recommended dosage for patients with documented *Pneumocystis carinii* pneumonitis is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. The following table is a guideline for the attainment of this dosage in children.

Weight		Dose —every 6 hours	
lb	kg	Teaspoonfuls	Tablets
18	8	1 (5 ml)	1/2
35	16	2 (10 ml)	1
53	24	3 (15 ml)	1 1/2
70	32	4 (20 ml)	2 (or 1 DS tablet)

HOW SUPPLIED: TABLETS, containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100.

ORAL SUSPENSION, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored—bottle of 450 ml. Also available in double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole—Compliance™ Pak of 20, bottle of 60 and unit dose pack of 100.

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C U R S O S

CLINICAL CYTOPATHOLOGY FOR PATHOLOGISTS - POSTGRADUATE COURSE

The Twenty-second Postgraduate Institute for Pathologists in Clinical Cytopathology is to be given at The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore, Maryland, March 22-April 3, 1981. The full two week program is designed for pathologists who are Certified (or qualified) by the American Board of Pathology (PA), or their international equivalents.

It will provide an intensive refresher in all aspects of the field of Clinical Cytopathology, with time devoted to newer techniques, special problems, and recent applications. Topics will be covered in lectures, explored in small informal conferences, and discussed over the microscope with the Faculty. Self-instructional material will be available to augment at individual pace. A loan set of slides with text will be sent to each participant for home-study during February and March before the Institute. Credit hours 125 in AMA Category I.

Application is to be made before January 28, 1981. For details, write: John K. Frost, MD, 610 Pathology Building, The Johns Hopkins Hospital, Baltimore, Maryland 21205, U. S. A.

The entire Course is given in English.

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“SIMPOSIO INTERAMERICANO DE MEDICINA”

December 10-13, 1980

Diciembre 10-13, 1980

Sheraton Bal Harbour Hotel

Miami Beach, Florida, U. S. A

HIGHLIGHTS:

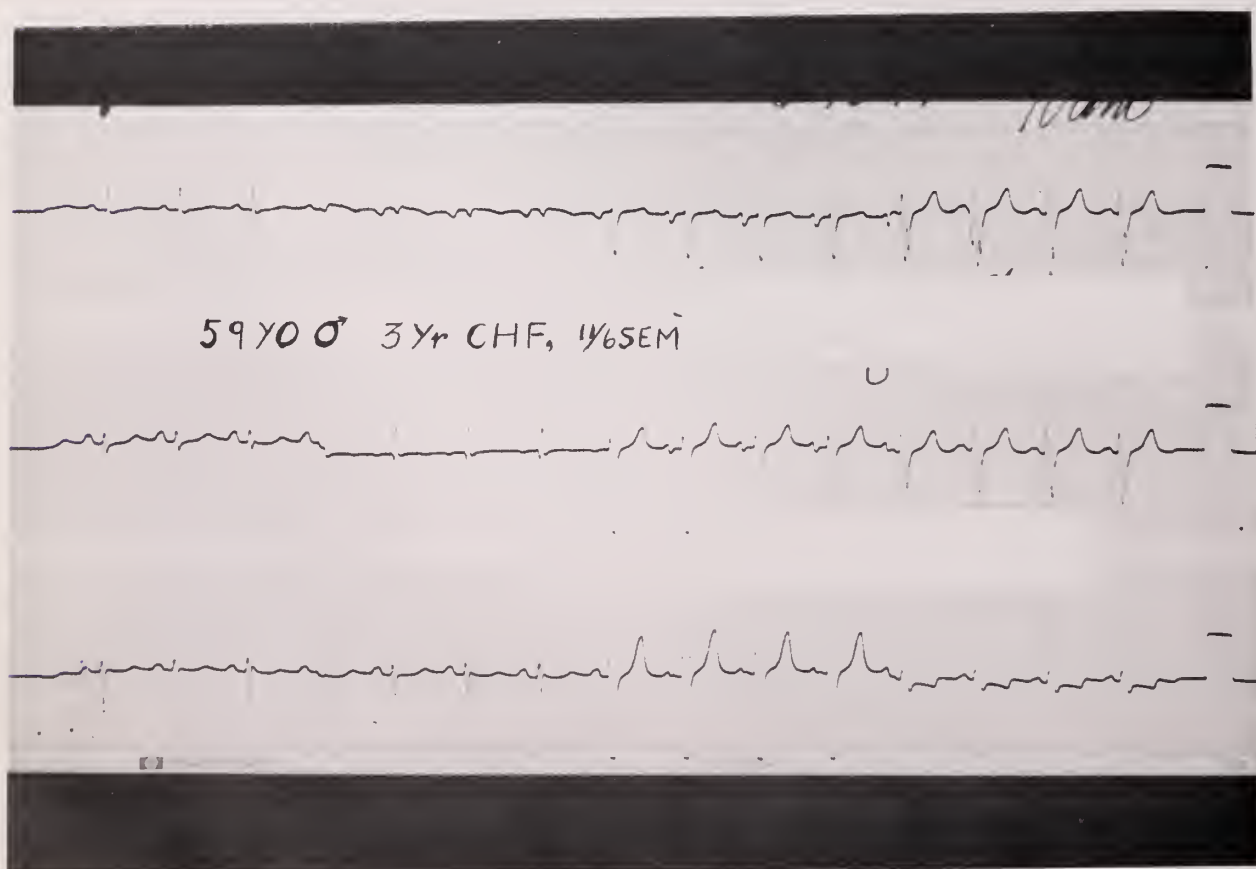
- * Speakers from 14 countries
- * 4 State of the Art Lectures
- * 15 Symposia
- * All Sessions in English and Spanish
- * Video Tape Evening Sessions
- * Audio-Visual Aids
- * Social Activities for Spouses and Children

EVENTOS DESTACADOS:

- * Disertantes de 14 países
- * 4 Actualizaciones
- * 15 Simposios
- * Todas las Sesiones en Inglés y Español
- * Sesiones Nocturnas de “Video Tapes”
- * Audio-Visuales
- * Actividades Sociales Para Miembros Titulares y Acompañantes

GRAPHICS

Este paciente varón de 59 años se presentó con un historial de disnea progresiva por tres años y ortopnea. Al examen físico el paciente demostró hallazgos de fallo congestivo con edema periférica, distensión de las venas del cuello y cardiomegalia. El pulso arterial era difícil de palpar, lento en el llenado y de poco volumen. La presión arterial 110/80 y la frecuencia cardíaca 100 por minuto. La auscultación cardíaca demostró un ritmo de galope ventricular (S3), un segundo sonido apagado y un soplo sistólico eyectivo en el 2do espacio intercostal derecho con radiación al cuello. El cardiograma y la radiografía de pecho están demostrados abajo.





El diagnóstico más probable es:

- A) Enfermedad hipertensiva cardiovascular
- B) Cardiomiopatía congestiva
- C) Estenosis aórtica valvular
- D) Estenosis mitral
- E) Insuficiencia mitral

CONTESTACION (C):

En este paciente el hecho de que el soplo sea sistólico elimina estenosis mitral ya que en estenosis mitral el soplo es diastólico. La característica eyectiva del soplo con la radiación a cuello nos debe alertar a un posible origen aórtico y no mitral.

La placa de pecho y el electrocardiograma demuestran cardiomegalia con hipertrofia de ventrículo y atrio izquierdo y cambios del segmento ST. Esto apunta a una sobrecarga de presión del ventrículo izquierdo aunque no elimina por completo la posibilidad de una cardiomiopatía congestiva. El hecho de que el segundo sonido esté apagado sugiere inmovilidad de la válvula aórtica. La presión arterial normal va en contra de enfermedad hipertensiva cardiovascular. Este paciente murió subsiguientemente, y la foto abajo revela una válvula aórtica severamente estenótica con un orificio valvular (indicado por la flecha) menos de 1 cm^2 (normal $4\text{-}6\text{ cm}^2$). Cuando el paciente con estenosis aórtica valvular desarrolla síntomas de fallo congestivo es un síntoma grave y el paciente debe ser referido para estudios invasivos y posible cirugía pues usualmente su pronóstico de vida es de menos de 3 años.



Guillermo Cintrón, MD, FACP
Director, Unidad Coronaria
Hospital de Veteranos

NOTICIAS

AMA NEWS:

SNUFF AND CHEWING TOBACCO CALLED HAZARDS TO HEALTH

Chicago - Smokeless tobacco — snuff and chewing tobacco — causes serious health problems, says a communication in the July 11 Journal of the American Medical Association.

Health warnings are required on cigarette packages, but not on boxes of snuff or plugs of chewing tobacco, despite the fact that snuff may be more dangerous to the mouth and throat than cigarettes, says Alan Blum, MD., Morris Fishbein Fellow on the Journal.

Some smokers who have had difficulty in breaking the addiction to nicotine have been turning to smokeless tobacco as less harmful to health than smoking tobacco. But smokeless tobacco also has hazards.

Snuff causes gum disease, tooth abrasion, white patches on the throat that sometimes become cancerous, and other health problems, says Dr. Blum. And chewing tobacco is even worse, causing cancers of the mouth, throat and digestive tract, he says.

Dr. Blum points to broadcast and print media advertising featuring well-known athletes and country-rock stars for various brands of snuff and chewing tobacco. The campaigns are directed at the youth market, he says, and use of both snuff and chewing tobacco is increasing.

SENILITY SOMETIMES CAUSED BY CURABLE AILMENTS

CHICAGO — Senility — the intellectual im-

pairment that may come with advancing years — sometimes is caused by curable physical and emotional disease, says a report in the July 18 Journal of the American Medical Association.

And even if senility is chronic and cannot be cured, there is much that can be done to help lessen the impact of the condition and make life more meaningful for those affected, the report says.

The report — titled “Senility Reconsidered” — is from a Task Force of experts, sponsored by the National Institutes of Aging, Bethesda, MD.

It is generally accepted that there are changes in some intellectual functions in the elderly, just as there is some loss in physical abilities with aging, the Task Force says.

“Normal aging, however, does not include gross intellectual impairment, confusion, depression hallucinations, or delusions. Such symptoms are due to disease and indicate the need for diagnosis and treatment.”

Estimates are that some 10 per cent of individuals older than 65 years have noticeable intellectual impairment. Some 10 to 20 per cent of those individuals having such impairment have reversible conditions that will improve with treatment.

Early symptoms of senile dementia as noted by relatives, employers or friends, and frequently by the patients themselves, are failing attention and memory and declining mathematical ability. Errors of judgment, irritability, personality changes, loss of sense of humor, or poor orientation may indicate that intellectual function is deteriorating.

This can be caused by certain conditions that cannot be cured. But also it can be caused by adverse effects of medications, and by illnesses involving heart, lungs, kidneys or liver, glandular imbalances, body fluids and minerals upsets, too little oxygen, anemia, infections, nutritional deficiencies, and becoming too hot or too cold, the Task Force points out. Many of these conditions can be corrected.

Even if the elderly patient has an irreversible disorder, as do many, frequently much can be done

to reduce the severity of its manifestations through treatment of the symptoms and supportive therapy. Those around the elderly person whose mind is failing must be aware that the patient has difficulty with orientation as to time, place and person, and needs to be constantly reminded.

Those with intellectual impairment should be kept in familiar surroundings if at all possible, as it is difficult for them to cope with unfamiliar places.

Doctors should be aware of the extreme sensitivity of the aged brain to a wide variety of medications. Ordinary doses sometimes lead to problems.

And finally:

"A key feature in maintaining mental health in old age seems to be continued mental as well as physical activity."

The Task Force is composed of Richard W. Besdine, MD, of the Hebrew Rehabilitation Center for the Aged and Harvard Medical School, Boston; MDs Jacob A. Brody, Robert N. Butler and Leroy E. Duncan of the National Institute on Aging of the National Institutes of Health, Bethesda; Lissy Jarvik, MD, of Brentwood Veterans Administration Medical Center and UCLA Medical School, Los Angeles, and Leslie Libow, MD, of the Jewish Institute for Geriatric Care and the State University of New York, Stony Brook.

POISONING REPORTED FROM POPULAR SEA FOODS

CHICAGO— Don't eat the barracuda, and stick to the little ones when eating grouper or red snapper. The health risk is ciguatera fish poisoning, and it will make you very sick.

Reports in the July 18 Journal of the American Medical Association detail outbreaks of the poisoning from eating reef fish caught off the Atlantic Coast of Florida several years ago. In Florida and Hawaii ciguatera poisoning is a sizeable public health problem.

If you should eat a piece of fish containing

the ciguatera toxin, the result will be diarrhea and vomiting, muscle pain, burning or prickling sensation in hands and feet, itchy skin, headache, dizziness, weakness. That is, you will be very ill. The attack is seldom fatal, however.

In a study of cases reported to the Dade County (Miami) Department of Public Health, grouper and snapper were the fish most frequently implicated. Most cases were in late spring and summer. Small fish seldom caused problems. Illness followed eating of portions cut from big fish.

Barracuda was so often involved in cases of ciguatera fish poisoning that sale of the fish commercially is now banned under the Miami City Code.

It is assumed that fish become toxic by eating smaller marine organisms containing the offending substance. Big fish eat the littler fish and thus accumulate large amounts of the poison, which does not disturb the fish itself. The toxin does not affect taste or appearance of the fish.

Cooking has no impact on the toxin, and neither does freezing. The fish market or restaurant serving the fish is not responsible, as the attack is not triggered by improper storage or handling.

Grouper is most often the culprit, causing 60 percent of the Southeastern Florida cases. Snapper is next most common with 14 per cent.

There isn't much public health authorities can do to reduce attacks of ciguatera fish poisoning, short of banning sale and eating of the offending fish. Since Floridians eat about 12 million pounds of grouper and red snapper annually, this would not be practical.

Ciguatera fish poisoning is common in the Caribbean and South Pacific. First reference to the illness was by a Spanish sea captain in 1555.

One test in the Pacific found that the toxin was present in more than two-thirds of red snapper weighing more than six pounds.

In an editorial, Charles P. Craig, MD, University of South Florida, Tampa, suggests that fishing be suspended for some time in the area of a coral reef that has been disturbed by construction of a wharf, pier or bridge. Consumption of smaller grouper or snapper is advisable. If large fish are eaten, the toxin may be diluted by soaking the flesh in repeated changes of water, Dr. Craig says.

The report is by Dale N. Lawrence, MD, of the

Center for Disease Control, Atlanta, working with the Dade County and Florida Departments of Health.

HEAVY DRINKERS AFFECTED BY POPULAR PAIN RELIEVER

CHICAGO — Acetaminophen — a popular nonprescription pain reliever) and heavy use of alcohol do not mix, says a report in the July 18 Journal of the American Medical Association.

Acetaminophen is available under several trade names — Tylenol, Phenaphen and Temptra — and is a useful product to relieve pain and reduce fever in those individuals who cannot take aspirin.

Craig J. McClain, MD, of the Veterans Administration Medical Center, Minneapolis, reports on severe liver failure that developed in three chronic alcoholics after taking excessive doses of acetaminophen to ease pain. All were seriously ill and one died.

Persons who regularly use alcohol frequently take acetaminophen instead of aspirin because of well-known gastrointestinal side effects of alcohol and aspirin combinations, Dr. McClain points out.

"It is thus necessary that both physicians and the general public be made aware of the potential increased risk for liver toxicity by this over-the-counter (nonprescription) drug," he concludes.

In an accompanying editorial, Robert M. Craig, MD, of Northwestern University Medical School, Chicago, says the same: "Patients should probably be warned that the coadministration of alcohol and acetaminophen, at least in high therapeutic doses, may be harmful."

Acetaminophen remains a useful product to cope with pain and fever. It does not help with the pain of arthritis. The American Medical Association's drug manual, AMA Drug Evaluations, 4th Edition, says that acetaminophen is the preferred drug to relieve pain and fever in those allergic to aspirin.

TREATMENT CAN HELP HAY FEVER SUFFERERS

CHICAGO — Many people will suffer the tortures of hay fever this fall. And much of the suffering could be avoided.

There have been predictions that the fall of 1980 will be an especially difficult time for hay fever sufferers, with an above-average pollen count following an unusually wet winter.

Most sufferers still fail to take full advantage of the available remedies, says a pamphlet on hay fever from the American Medical Association.

The most common causes of hay fever and asthma are pollen, molds and insect particles, the AMA leaflet says. There usually are three seasons. The spring season, in April and May, is caused by the pollen of such trees as maple, elm, poplar, birch and oak. The midsummer season is caused by grasses, such as timothy, bluegrass, Bermuda, and Johnson.

It is the fall type of hay fever which is responsible for the most frequent and severe suffering, the AMA points out.

Fall hay fever is produced most often by the ragweeds.

Weather makes a difference. When it is sunny, hot and windy, there is much pollen in the air and hay fever symptoms are severe. Cool, cloudy and rainy weather diminishes pollen.

A change in climate is far from a cureall. You may escape one allergen only to find others present in the new location.

The most effective preventive treatment for severe hay fever is shots, says the AMA pamphlet. This means regular injections of solutions of pollen or other allergy-producing substances, beginning with tiny doses. As the doses increase, the antibodies become sufficient to counteract the harmful substance. Desensitization is not a quick process. A few people may get some relief in three or four shots, but usually it takes weeks or months to note results.

AMA Drug Evaluations, the AMA's manual for physicians, points out that antihistamines are effective in the management of hay fever symptoms.

Some 70 to 95 per cent of patients experience some relief from runny nose, sneezing, and watery, swollen eyes. There are long-acting preparations that can be taken at bedtime to control the more severe symptoms that are usually evident in the early morning, the AMA book says.

Therapy with antihistamines should be started at the beginning of the hay fever season while pollen counts are still low. If therapy is delayed, the temporary use of an aerosol corticosteroid preparation may be required to control symptoms.

ELECTRONIC FETAL MONITORING CALLED LIFE-SAVING TECHNIQUE

CHICAGO — Electronic fetal monitoring (EFM) is a valuable asset in management of pregnancy and labor, says a report in the Aug. 15 Journal of the American Medical Association.

EFM has been challenged recently as unnecessarily invasive of the expectant mother and the unborn child, and also as too expensive, Orvan W. Hess, MD, of Yale University Medical School, New Haven, Conn., points out.

Dr. Hess cites a number of studies of EFM which support the belief that it has resulted in saving lives and decreasing the risk of brain damage that may result from oxygen being cut off to the fetus during labor.

The use of EFM for the fetus at risk can aid in timing intervention to favor optimum safety for mother and infant, Dr. Hess declares.

"Such benefits to society seem to justify the added cost and continued use of EFM. One can predict, in view of advances in electronics that bio-engineers, physicians, and industry, working together, will meet the challenge to provide better and less costly equipment."

EFM equipment improves detection of fetal

heart beat and uterine contractions. A change in fetal heart beat may indicate impairment of circulation of oxygen-carrying blood to the fetus, with potential damage to the infant, possibly stillbirth, he says.

The careful electronic monitoring permits the doctor to know instantly when the delivery is in trouble and take steps to correct the problem before damage is done to the infant.

EPILEPSY DRUG CURBS SEIZURES AND IMPROVES BEHAVIOR

CHICAGO — Usefulness of valproic acid in controlling epilepsy seizures and improving behavior is affirmed in a report in the Aug. 22/29 Journal of the American Medical Association.

Valproic acid has been on the market for more than two years, and already had been established as safe and effective. David L. Coulter, MD, University of Michigan Medical School, Ann Arbor, reports on use of valproic acid alone or in combination with other anticonvulsant drugs in 100 children with epilepsy.

Mean improvement of the children in seizure control was 82 per cent, Dr. Coulter says. Petit mal seizures responded best, but other types of seizures, even with associated mental and physical handicaps, also responded well, he says.

The changes in alertness and behavior were striking, the Michigan physician reports. Forty-three children were noticeably improved, and for some the benefit was truly remarkable. Comments include: "He has learned more in one week than he had in the past three years," "It is like having a new child in the family," and "He is now discovering the world he has been sleeping through."

For most patients, Dr. Coulter reports, the improvement could be attributed to reduced seizures or reduced dosages of sedatives, but three children were more alert despite having frequent seizures and

continued high dosages of sedating drugs.

Eighty per cent of the children in the study achieved at least 50 per cent reduction in seizures from valproic acid, and it "is an extremely effective agent when children have uncontrolled seizures of

any type."

Dr. Coulter adds that since preparing the report the 100 children have been followed six more months, with continuing favorable results.

Trade name of valproic acid is Depakene.

ANUNCIO

APERTURA DE OFICINA:

Tomás Febo Rodríguez, M. S., CCC/SP
Patólogo del Habla y Lenguaje
Diplomado del "American Speech Language & Hearing
Association" (ASHA)

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y Lectura

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Ave. Muñoz Rivera 500
Hato Rey, P. R. 00918

Teléfono 762-9177

Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Immunizations Guard Against Many Ills

Vaccines Halt Ills

The current popular emphasis in health care is positive health programs and preventive medicine.

Positive health programs for the most part are up to you. Keep your weight down, exercise regularly, eat a wide variety of foods in moderation, don't smoke, use alcohol sparingly, seek a healthy mental approach to stress.

But preventive medicine involves your doctor and includes immunizations. Of course, here again it's up to you to go to the doctor and ask about immunizations. But he or she will give them.

Immunization is a priceless health asset, says a pamphlet from the American Medical Association. Vaccines to prevent diphtheria, tetanus and typhoid fever have been available for many years. The smallpox vaccine worked so well that the disease has been eliminated, and this vaccination no longer is needed.

Whooping cough, polio and flu vaccines were added in later years. And now we have vaccines to protect

against measles, German measles and mumps.

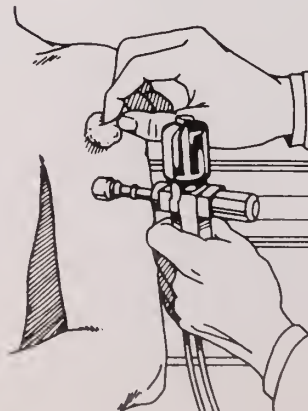
Diphtheria, tetanus and pertussis (whooping cough) is given in one dose, beginning as early as age two months, with occasional booster doses. Polio vaccine also is given starting at two months, with boosters later. German measles (rubella) is given after one year of age and boosters probably are not needed. Mumps also is given at the age of one year, as is measles (rubeola).

Typhoid vaccine is given only when needed, during exposure to unsafe water supplies. This vaccine is not given routinely in the United States.

Influenza vaccine is recommended annually for persons with chronic debilitating conditions. It is not given to those who are hypersensitive to eggs. A pneumococcus vaccine is also available now to protect the elderly and chronically ill against pneumonia.

For foreign travel, other vaccinations may be recommended, such as yellow fever, plague, cholera and typhus. Local health departments or your doctor can give details.

Prevention of disease through immunization is a personal health responsibility. Every family is responsible for the adequate protection of its own members against those diseases for which immunization is available. Your doctor can give the shots only if you go and ask.



October, 1980
Frank Chappell
Science News Editor
AMA

ROCHE

For recurrent attacks of urinary tract infection in women

Bactrim™ DS Double Strength Tablets

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Just one tablet b.i.d. for 10 to 14 days



- Action at urinary/vaginal/lower bowel sites helps eliminate reservoirs of infecting organisms
- Distinctive antibacterial action plus wide spectrum helps eradicate recurrent UTI
- Low incidence of bacterial resistance in community practice

- Convenient *b.i.d.* dosage provides day-and-night antibacterial control
- Contraindicated during pregnancy and the nursing period. During therapy, maintain adequate fluid intake; perform CBC's and urinalyses with microscopic examination.

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morganii*. **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.** Note: The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

Also for the treatment of documented *Pneumocystis carinii* pneumonia. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

The recommended quantitative disc susceptibility method (*Federal Register*, 37:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers; infants less than two months of age.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. **Blood dyscrasias:** Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. **Allergic reactions:** Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. **Gastrointestinal reactions:** Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. **CNS reactions:** Headache,

peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. **Miscellaneous reactions:** Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

Urinary Tract Infections: Usual adult dosage—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Recommended dosage for children—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

***Pneumocystis carinii* pneumonia:** Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: Double Strength (DS) tablets, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, Tel-E-Dose® packages of 100 Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. Oral suspension, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).



Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Please see back cover.

Her next attack of cystitis may require

the Bactrim 3-system counterattack



ROCHE

Bactrim has shown high clinical effectiveness in recurrent cystitis as a result of its wide spectrum and distinctive antimicrobial action in the urinary, vaginal and lower intestinal tracts.

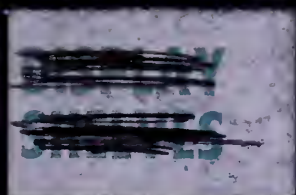
The probability of recurrent urinary tract infection appears to be enhanced by the establishment of large numbers of *E. coli* or other urinary pathogens on the vaginal introitus. The trimethoprim component of

Bactrim diffuses into vaginal fluid in effective concentrations, thus combating migration of pathogens into the urethra.

Studies have shown that Bactrim acts against *Enterobacteriaceae* in the bowel without the emergence of resistant organisms. Thus, Bactrim reduces the risk of introital colonization by fecal uropathogens. It has no significant effect on other normal, necessary intestinal flora.

Bactrim fights uropathogens in the urinary tract/vaginal tract/lower intestinal tract

Please see reverse side for summary of product information.



BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

CONTENIDO:

LAS CEFALOSPORINAS - PROGRESO TERAPEUTICO

ISONIAZID (INH) CYSTITIS

SEXUALLY TRANSMITTED DISEASES - PART II
SYPHILIS, CHLAMYDIAS, HERPES AND SCABIES

EDITORIAL: FUTURO Y PERSPECTIVAS DE LAS
ENFERMEDADES INFECCIOSAS EN PUERTO RICO

CARTA AL EDITOR: ANOTHER GREAT DECEIVER -
INTRAPLEURAL MESOTHELIOMA

ABSTRACTOS DE LITERATURA MEDICA

MEDI-QUIZ

BRIEF COMMUNICATION: SCORING BEFORE THE
BIG GAME DOES NOT TAKE AWAY FROM AN
ATHLETE'S PERFORMANCE

CURSOS - NOTICIAS

INDICE PAGINA 518

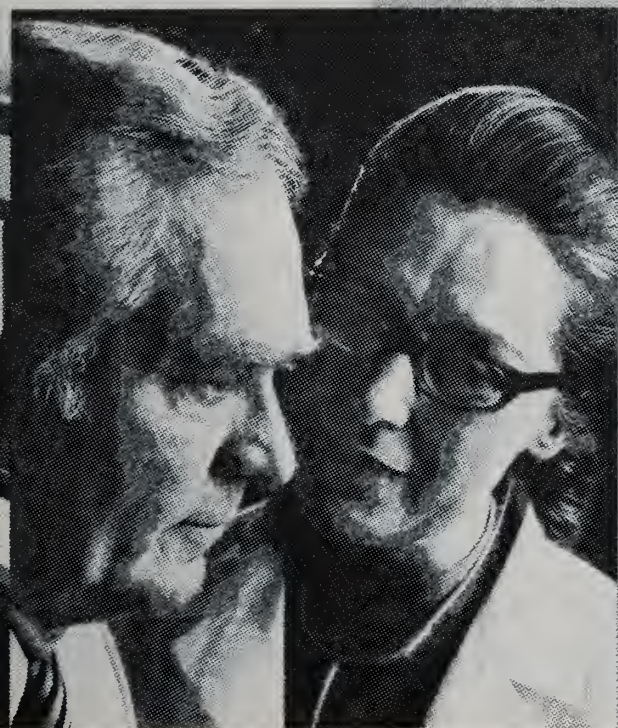
THE FRANCIS A. COWNTWAY
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10 CHATLICK STREET



proven antianxiety

Highly specific calming action
virtually free of unwanted
side effects: this was the remarkable
clinical promise of Librium (chlordiazepoxide HCl).
And today this promise continues to be
fulfilled in a wide variety of patients
you see every day.





The published record on Librium is enormous. So large, in fact, it had to be put into a computer data bank and retrieval system. It's a record that shows Librium is highly effective in relieving anxiety; that Librium is seldom associated with serious side effects; that Librium rarely interferes with mental acuity at proper doses; that Librium is used concomitantly with primary medications. However, as with all CNS agents, patients should be warned against hazardous activities requiring complete alertness, and about possible combined effects with alcohol.

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON

JAN 16 1981

performance

Librium[®] *®*
chlordiazepoxide HCl/Roche



5mg, 10mg, 25mg capsules

***synonymous
with relief
of anxiety***

- ☐ An unsurpassed safety record
- ☐ Minimal effect on mental acuity, in proper dosage
- ☐ Predictable patient response
- ☐ Is used concomitantly with primary medications, such as anticholinergics and cardiovascular drugs

Please see next page for summary of product information.

Librium® 5mg, 10mg, 25mg capsules chlordiazepoxide HCl/Roche

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended

Contraindications: Patients with known hypersensitivity to the drug

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage, withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

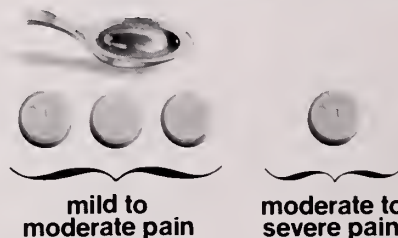
Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral-Adults:* Mild and moderate anxiety and tension, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. *Geriatric patients:* 5 mg b.i.d. to q.i.d. (See Precautions.)

Supplied: Librium® (chlordiazepoxide HCl) Capsules, 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Libritabs® (chlordiazepoxide) Tablets, 5 mg, 10 mg and 25 mg—bottles of 100 and 500. With respect to clinical activity, capsules and tablets are indistinguishable.

TYLENOL® with Codeine tablets & elixir



Summary of Prescribing Information

Description

Tablets: Contain codeine phosphate* No. 1—7.5 mg (1/4 gr.); No. 2—15 mg (1/2 gr.); No. 3—30 mg (1/2 gr.); No. 4—60 mg (1 gr.)—plus acetaminophen 300 mg

Elixir: Each 5 ml. contains 12 mg. codeine phosphate* plus 120 mg. acetaminophen (alcohol 7%).

*Warning: May be habit forming

Actions: Acetaminophen is an analgesic and antipyretic; codeine an analgesic and antitussive.

Contraindications: Hypersensitivity to acetaminophen or codeine

Warnings: *Drug dependence:* Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration, prescribe and administer with same caution appropriate to other oral narcotics. Subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Caution patients that codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other CNS depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with this drug may exhibit additive CNS depression. When such a combination is contemplated, reduce the dose of one or both agents.

Usage in pregnancy: Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.

Pediatric use: Safe dosage of this combination has not been established in children below the age of three.

Precautions: *Head injury and increased intracranial pressure:* Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: Codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients: Administer with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: Most frequent: lightheadedness, dizziness, sedation, nausea and vomiting, more prominent in ambulatory than nonambulatory patients, some of these reactions may be alleviated if the patient lies down. Others: euphoria, dysphoria, constipation and pruritus.

Dosage and Administration: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. **TYLENOL with Codeine tablets** are given orally. The usual adult dose is: Tablets No. 1, No. 2, and No. 3. One or two tablets every four hours as required. Tablets No. 4. One tablet every four hours as required. **TYLENOL with Codeine elixir** is given orally. The usual doses are **Children (3 to 6 years):** 1 teaspoonful (5 ml.) 3 or 4 times daily; **(7 to 12 years):** 2 teaspoonful (10 ml.) 3 or 4 times daily; **(under 3 years):** safe dosage has not been established. **Adults:** 1 tablespoonful (15 ml.) every 4 hours as needed.

Drug Interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings. For information on symptoms/treatment of overdosage, see full prescribing information.

Full directions for use should be read before administering or prescribing

TYLENOL with Codeine tablets are manufactured by McNeil Laboratories Co., Dorado, Puerto Rico 00646

Caution: Federal law prohibits dispensing without prescription.

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No. 1—7.5 mg (1/8 gr); No. 2—15 mg (1/4 gr); No. 3—30 mg (1/2 gr); No. 4—60 mg (1 gr)
Elixir Each 5 ml contains 12 mg codeine phosphate* plus 120 mg acetaminophen (Alcohol 7%)

*Warning: May be habit forming

Please see facing page for summary of prescribing information

New evidence is in: Treatment of mild hypertension can save lives

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- Of nearly 11,000 hypertensives identified by the Hypertension Detection and Follow-up Program, slightly more than 70% had mild hypertension (DBP 90-104 mm. Hg).¹
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**The primary agent used by the HDFP
in an effective low dose**

Hygroton[®] 25 mg.
(chlorthalidone USP)
one a day

**Because there's nothing mild
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BRIEF SUMMARY

Indications: Hypertension; adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and

related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily. **How Supplied:** Tablets—100 mg (white, scored), 50 mg (aqua) in bottles of 100, 1000 and 5000; 25 mg (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:

1. Five-year Findings of the Hypertension Detection and Follow-up Program. 1. Reduction in Mortality of Persons With High Blood Pressure, Including Mild Hypertension, JAMA 242: 2562, Dec. 7, 1979 2. Payne, G H.: Presentation of HDFP findings (Nov. 27, 1979), data on file, USV Laboratories.

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ASOCIACION MEDICA DE PUERTORICO

VOLUMEN 72

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NUMERO 10

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*José Juan Gutiérrez Núñez, MD, Paul Terence Harrington, MD,
Rafael Quiñones Soto, MD, Ramón H. Bermúdez, MD, FACP y
Carlos H. Ramírez Ronda, MD, FACP*

Al momento presente tenemos disponible por lo menos 14 derivados semi-sintéticos de la cefalosporina C., producida por el hongo *cefalosporium acremonium*.

En esta edición Gutiérrez-Núñez y colaboradores revisan la farmacología, mecanismo de acción, indicaciones, clasificación y efectos secundarios de este grupo de antibióticos.

- * **Isoniazid (INH) Cystitis** 527
Nicholas Tiliakos, MD, A. Rafael Morales, MD and Steve Tsoukalos, MD

Isoniazid (INH) is metabolized by acetylation to acetylisoniazid. In slow acetylators, 63 percent of INH is metabolized by acetylation. In fast acetylators, 94 percent is excreted as acetylisoniazid. Depending on the acetylator phenotype, free INH and its hydrazone derivatives are also excreted in the urine. In this issue, a 20-year old male with hemorrhagic cystitis secondary to hydrazone INH derivatives is presented. The author present pharmacologic evidence which, in my opinion support their conclusions. Although extremely rare, INH cystitis depends both on the individual acetylator phenotype and a localized idiosyncratic reaction in the bladder.

- * **Sexually Transmitted Diseases: Part II - Syphilis, Chlamydias, Herpes and Scabies** 530
*Carlos H. Ramírez Ronda, MD, FACP, José J. Gutiérrez-Núñez, MD,
Ramón H. Bermúdez, MD, FACP, Guillermo Vázquez, MD, Rafael
Quiñones, MD, Zelma Fuxench-Chiesa, MD, Julie Rodríguez, MD,
Nilda Hernández, MD, José Maldonado, MD and Paul T. Harrington, MD*

In this issue, Ramírez Ronda and co-workers present the current status of the diagnosis, pathogenesis and treatment of the most relevant and clinically important sexually transmitted diseases. At a time when there appears to be an increase incidence of syphilis and gonorrhea, this review article should be of interest to all. The bibliography, although complete up to 1978, doesn't contain pertinent references published in the last year.

- * **Editorial: Futuro y Perspectivas de las Enfermedades Infecciosas en P. R.** 543
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LAS CEFALOSPORINAS PROGRESO TERAPEUTICO

José Juan Gutiérrez-Núñez, MD, Paul Terence Harrington, MD
Rafael Quiñones Soto, MD, Ramón H. Bermúdez, MD, FACP
y Carlos H. Ramírez Ronda, MD, FACP

Introducción

Las cefalosporinas son un grupo de antibióticos beta lactámicos que son utilizados con mucha frecuencia por su amplio espectro antimicrobiano y baja-toxicidad (1-14). Todas las cefalosporinas son derivados semi-sintéticos de la cefalosporina C, la cual es producida por el hongo *Cephalosporium acremonium* (5).

Con la introducción en el 1962 de cefalotina se comienza la búsqueda de otras cefalosporinas modificando la estructura molecular del núcleo de ácido cefalosporínico. Este núcleo se puede modificar en varios lugares: 1. En la posición 7 del anillo beta lactámico lo cual provee mayor actividad antimicrobiana y resistencia a las beta lactamasas (6). 2. En la posición 3 del anillo de dehidrotiazina lo cual produce cambios en las propiedades far-

macocinéticas y metabólicas (7). Sustituyendo radicales químicas en ambas posiciones se alteran las características generales de su estructura y función. Estas alteraciones en el anillo cefalosporínico han producido un nuevo grupo de cefalosporinas con diferentes rutas de administración, farmacocinética y espectro antimicrobiano (8-14). En la Tabla I se presenta una lista de las cefalosporinas actualmente disponibles y aquellas que lo estarán en un futuro cercano.

Como grupo las cefalosporinas tienen varias propiedades importantes: 1. Son bactericidas. 2. Son relativamente resistentes a la beta lactamasas producida por el *Staphylococcus aureus*. 3. Poseen actividad de amplio espectro antimicrobiano, esta actividad varía entre las cefalosporinas de la primera, segunda y tercera generación para bacilos gram-negativos, y 4. Poseen un índice de toxicidad baja. Presentamos las propiedades generales, las similitudes básicas y diferencias importantes entre las cefalosporinas como grupo, y las propiedades específicas en detalle de algunas de ellas.

Del Programa de Entrenamiento en Enfermedades Infecciosas, Hospital de Veteranos y Escuela de Medicina de la Universidad de Puerto Rico, y Hospitales Afiliados y Laboratorio de Enfermedades Infecciosas y Servicios de Investigación y Medicina del Hospital de Veteranos y Departamento de Medicina de la Escuela de Medicina de la Universidad de Puerto Rico, San Juan, Puerto Rico.

Favor de pedir reimpresos a: Carlos H. Ramírez Ronda, MD, FACP, Hospital de Veteranos, Programa de Enfermedades Infecciosas (151), GPO Box 4867, San Juan, Puerto Rico 00936.

Mecanismo de Acción y Farmacología

Las cefalosporinas al igual que las penicilinas, interfieren con la síntesis de la pared celular. La estructura molecular del

TABLA I

<i>Nombre Genérico</i>	<i>Nombre Comercial</i>	<i>% unión proteínas séricas</i>
<i>Cefalotina</i>	<i>Keflin</i>	65-79
<i>Cefaloridina</i>	<i>Loridine</i>	10-31
<i>Cefazolina</i>	<i>Ancef, Kefzol</i>	74-86
<i>Cefapirina</i>	<i>Cefadyl</i>	44-50
<i>Cefacetrile</i>	<i>Celespor</i>	35
<i>Cefradina</i>	<i>Velosef, Anspor</i>	6-20
<i>Cefaloglicina</i>	<i>Kafocin</i>	-----
<i>Cefalexina</i>	<i>Keflex</i>	10-15
<i>Cefaclor</i>	<i>Ceclor</i>	-----
<i>Cefadroxil</i>	<i>Duricef</i>	-----
<i>Cefamandole</i>	<i>Mandol</i>	70
<i>Cefoxitina</i>	<i>Mefoxin</i>	73
<i>Cefotaxime</i>	-----	-----
<i>Moxalactam</i>	-----	-----

núcleo cefalosporínico tiene similitudes a la del complejo alanil-alanina. Este complejo integra la estructura básica de la pared celular bacteriana. Teniendo estructuras moleculares similares, las cefalosporinas impiden la acción de las enzimas peptidoglican transpeptidasa y D-alanina-carboxipeptidasa, previniendo la incorporación a la pared celular bacteriana de nuevos complejos N-acetil murámico-N-acetil glucosamina, y la formación de la reacción de transpeptidación que da rigidez a la pared celular bacteriana (15). Estos antibióticos inhiben la síntesis de la pared celular bacteriana y son agentes bactericidas.

Las cefalosporinas tienen una estructura molecular similar a la de la penicilina. El anillo beta lactámico es crucial para su actividad antimicrobiana; difieren de las penicilinas en que tienen un anillo de dehidrotiazina de seis determinantes mientras que el anillo de la penicilina es un anillo de thiazolidina de

cinco determinantes (4).

Las cefalosporinas difieren entre sí por sustituciones de varios radicales en diferentes posiciones moleculares. Son estas sustituciones las que le dan propiedad distintas. Los compuestos que tienen un grupo acetilo como cefalotina, cefacetrile y cefapirina son parcialmente metabolizadas en vivo a la forma de-acetilada. Este metabolito tiene menor actividad antimicrobiana (16). Todas las otras cefalosporinas no son metabolizadas y se excretan sin cambios en su estructura. Todas las cefalosporinas se eliminan por vía renal en forma rápida por medio de filtración glomerular y secreción tubular (17, 19). Entre el 60 por ciento y 100 por ciento de la dosis administrada se recupera en la orina en 24 horas (20). La concentración sérica que se obtiene después de la administración de 1 gramo intramuscular de la mayoría de las cefalosporinas es de 15 a 25 µg/ml (2). Se obtienen concen-

traciones más altas si se administran por vía endovenosa. La media vida para la mayoría de las cefalosporinas es de 30-60 minutos (2). La unión a proteínas séricas de cefazolina, cefalotina, cefamandole y cefoxitina es más alta que la unión a proteínas séricas de cefaloridina, cefalexina y cefradina (Tabla I). Las cefalosporinas se distribuyen a todos los tejidos y líquidos del cuerpo, con excepción del líquido cefaloraquídeo, esto permite usarlas en una variedad de infecciones. Se obtienen concentraciones adecuadas en el espacio y/o líquido pleural (21), pericárdico (22), ascítico (23) y sinovial (23). La penetración a líquido cerebrospinal es pobre (24, 25) y en la bilis se obtienen concentraciones casi iguales a las séricas (26). Cuando hay obstrucción en el tracto biliar no se obtienen concentraciones terapéuticas con ninguna de las cefalosporinas (26). No hay ventajas entre las cefalosporinas de primera y segunda generación si tomamos en consideración la dosificación recomendada, toxicidad, concentración sérica, media vida y unión a proteínas. Las cefalosporinas de tercera generación y las cefamicinas ofrecen ciertas ventajas en cuanto a su actividad antimicrobiana en contra de micro-organismos específicos.

Espectro Antimicrobiano

Las cefalosporinas son antibióticos de amplio espectro que tiene actividad en contra de micro-organismos gram-positivos y gram-negativos. Son efectivas en contra de la mayoría de los estafilococos, pneumococos y estreptococos (1). Ninguna cefalosporina tiene actividad en contra del enterococo. La mayoría de las cepas de *E. Coli* y *Proteus mirabilis* son inhibidas por casi todas las cefalosporinas (1). Otros bacilos gram-negativos como son *Klebsiella*, *Enterobacter*, los *Proteus* índole positivos (*rettgerie*, *morganii*, *vulgaris*), *Providen-*

cia y *Serratia* son resistentes en diferentes grados a las cefalosporinas de la primera generación. Muchas de estas cepas son susceptibles a las cefalosporinas de segunda generación como el cefamandole y cefoxitina (27-29). Las *Pseudomonas* son resistentes a todas las cefalosporinas, son efectivas en contra de los micro-organismos anaeróbicos con excepción de la mayoría de los *Bacteroides fragilis* (3). Cefoxitina, una cefamicina, tiene actividad en contra del 83 por ciento de las cepas de *Bacteroides fragilis* (31). Cefaclor y cefamandole tienen actividad en contra de *Haemophilus influenzae*, incluyendo las cepas resistentes a ampicilina (11-32).

Indicaciones

Las cefalosporinas son raramente recomendadas como tratamiento de primera elección, aunque son ampliamente utilizadas (Tabla II). Pueden sustituir a las penicilinas en la mayoría de los pacientes con historial de alergia no anafiláctica a penicilina. Debe reconocerse que hay reacción cruzada entre las penicilinas y las cefalosporinas en 10 por ciento de los pacientes (33). Las cefalosporinas no están indicadas en pacientes con alergia a penicilina que han tenido anafilaxis o en pacientes con la prueba de piel positiva con determinantes menores. Las cefalosporinas son agentes efectivos en el tratamiento de infecciones por cocos gram-positivos con la excepción del enterococo y algunas cepas de *Staphylococcus epidermidis* y *Staphylococcus aureus* resistentes a la meticilina (34-35). Por la alta frecuencia de *Staphylococcus aureus* y *Staphylococcus epidermidis* en la endocarditis temprana de válvula protésica, algunos autores recomiendan una cefalosporina o una penicilina resistente a penicilinasa como profilaxis durante cirugía de

TABLA II

Indicaciones de las Cefalosporinas

Se pueden utilizar

1. *Infecciones por Staphylococcus aureus*
2. *Infecciones por Staphylococcus epidermidis cuando su sensibilidad se ha demostrado.*
3. *Infecciones por estreptococos (excepción enterococo)*
4. *Infecciones por Enterobacteriaceae cuando su sensibilidad se ha demostrado in vitro*
5. *Infecciones del tracto urinario por micro-organismos susceptibles*
6. *Sustitución de penicilinas en pacientes alérgicos*
7. *Profilaxis en contra de Staphylococcus aureus y Staphylococcus epidermidis en cirugía de válvulas prostéticas y reemplazo de cadera*

No deben utilizarse

1. *Profilaxis de fiebre reumática*
 2. *Infecciones del sistema nervioso central*
 3. *Infecciones causadas por enterococos, pseudomonas y Bacteroides fragilis **
 4. *Pacientes alérgicos a penicilinas con historial de anafilaxis*
-

* 83 por ciento de las cepas *B. fragilis* son susceptibles a cefoxitina

re-emplazo valvular (36).

Las cefalosporinas son agentes efectivos en contra de las enterobacterias. Pueden utilizarse en las infecciones del tracto urinario. Es importante enfatizar que en infecciones serias usualmente acompañadas por bacteremias asociadas o causadas por bacilos gram-negativo debe utilizarse un aminoglucósido, en adición a las cefalosporinas hasta que el

laboratorio informe las susceptibilidades del micro-organismo. La actividad de cefaclor y cefamandole en contra de *H. influenzae* (11, 32), hace que se considere cefaclor en el manejo de niños con otitis media (37, 38), y se considera cefamandole en pacientes con infecciones respiratorias bajas, especialmente adultos con episodios asociados a enfermedad pulmonar crónica (32). Se ha demostrado

TABLA III

Nombre	Media vida (min)	Concentración Séricas ug/ml *	Ruta Administración	Dosis
Cefalotina	30-50	15-21	Parenteral	.5-2.0gm q4-6h
Cefaloridina	66-90	38	Parenteral	.5-1.0gm q8h
Cefazolina	96-120	52-76	Parenteral	.5-1.0gm q6-8h
Cefapirina	37	15-24	Parenteral	2.0gm 4-6h
Cefacetrile	33	22	Parenteral	-----
Cefradina	42	22	Oral	250-500mg q6h
Cefaloglicina	--	---	Oral	250mg q6h
Cefalexina	36-54	13-18	Oral	250-500mg q6h
Cefaclor	60-90	17	Oral	250-500mg q8h
Cefadroxil	---	---	Oral	500mg q12h
Cefamandole	50-125	20-30	Parenteral	.5-2.0gm q4-6h
Cefoxitina	41	22-23	Parenteral	.5-2.0gm q4-6h
Cefotaxime	---	---	Parenteral	-----
Moxalactam	---	---	Parenteral	-----

* - Concentraciones séricas después de la administración de 1,000 mg I.M. o 500 mg oral.

la efectividad de cefoxitina en contra de *Neisseriae gonorrhoeae* incluyendo las cepas productoras de penicilinasas resistentes a penicilina (39).

Es importante enfatizar que las cefalosporinas no se utilizan en el manejo de infecciones del sistema nervioso central, debido a que su penetración al líquido cefalorraquídeo es pobre (24, 25).

Dosificación

Las dosis recomendadas se demuestran en la Tabla III. Para infecciones serias se recomiendan las dosificaciones más altas y los

intervalos más frecuentes de administración. La dosificación de cefalotina, cefradina y cefapirina se pueden intercambiar; cefazolina se administra en una dosis menor e intervalos menos frecuentes por su media vida más prolongada y una unión a proteínas séricas elevada. La dosificación de cefoxitina y cefamandole es similar a otras cefalosporinas. Las cefalosporinas orales se absorben predeciblemente bien; la dosificación es similar y la ingestión de comida no afecta su absorción (40). Cefadroxil, una cefalosporina oral, se administra cada 12 horas pero su uso se limita a infecciones del tracto urinario (41-45).

Efectos Secundarios

Reacciones por hipersensibilidad se ob-

serva en un 5 por ciento a 10 por ciento de los pacientes con las penicilinas: exantemas maculopapulares, urticaria, fiebre, enfermedad del suero y otras. Es relativamente frecuente notar que pacientes recibiendo cefalosporinas pueden desarrollar positividad en la prueba de Coombs sin evidencia de hemólisis (47). Trombocitopenia y neutropenia aunque infrecuente pueden ser severas, más usualmente son reversibles (48). Se han reportado alteraciones transitorias en las transaminasas hepáticas y nefritis intersticial; flebitis es otro efecto secundario relacionado con administración endovenosa; no hay evidencia contundente que una cefalosporina sea más o menos irritante que otra (49). Todas las cefalosporinas en dosis mayores que las recomendadas tienen un potencial de nefrotoxicidad, el ejemplo clásico es la cefaloridinas (50). Hay evidencia que la administración de una cefalosporina más un aminoglucósido es más nefrotóxico que una penicilina más un aminoglucósido (19, 46, 51). Cuando se utilizan ambos antibióticos la función renal debe seguirse cerca. Las cefalosporinas pueden dar una prueba falso positivo de azúcar cuando se utilizan los métodos de Benedict, Fehling y Clinitest.

Cefalosporinas Orales

Cefalexina y Cefradina

Cefalexina y cefradina sustituyen a cefaloglicina ya que este último agente no lograba concentraciones séricas adecuadas y se utilizaba únicamente en infecciones del tracto urinario. Estos agentes al administrarse por vía oral se obtienen concentraciones séricas adecuadas. No hay diferencias significativas entre estas dos cefalosporinas en cuanto a espectro anti-microbiano y farmacocinética (52). Se pueden utilizar en pacientes con infecciones de tejido blando que no pueden

recibir una penicilina. Se pueden utilizar para completar un curso prolongado de tratamiento en pacientes que no requieren el uso continuado de una cefalosporina parenteral y que tengan un micro-organismo causando la infección que sea susceptible. Se pueden utilizar en infecciones de vías urinarias causadas por cepas de *E. Coli*, *P. mirabilis* y *K. pneumoniae* resistentes a sulfonamidas o ampicilina pero sensitivas a cefalexina o cefradina. Las dosis recomendadas son de 250mg a 500mg cada seis horas hasta un máximo de cuatro gramos al día.

Cefaclor

Cefaclor es una cefalosporina oral que se introdujo recientemente al mercado. Su farmacología y actividad in vitro es similar a la de las otras cefalosporinas orales con las siguientes excepciones: 1) La actividad aumentada en contra de cepas de bacilos gram-negativos como *Klebsiella*, *Enterobacter*, *Proteus* y *Citrobacter*, muy similar a la actividad de cefamandole (11, 52). 2) Su actividad en contra de *Haemophilus influenzae*, la cual es ocho veces mayor que cefalexina y cefradina incluyendo cepas que producen beta lactamasas, aunque se han encontrado algunas cepas que son resistentes a cefaclor. 3) Estudios han demostrado que se obtienen concentraciones adecuadas en oído medio iguales o similares a las obtenidas con amoxicilina (37, 38). Esto hace al cefaclor un antibiótico de gran utilidad para infecciones en la edad pediátrica. Las dosis recomendadas en el adulto son de 250mg cada ocho horas hasta un máximo de cuatro gramos al día. En niños se recomienda 20mg/kg/día divididos en tres dosis cada ocho horas; se puede aumentar hasta 40mg/kgd/día en otitis media; no se debe exceder de un gramo por día. Además el cefaclor se recomienda para infecciones urinarias, infecciones del tejido blando e infeccio-

nes del tracto respiratorio causadas por micro-organismos susceptibles.

Cefadroxil

Cefadroxil es una cefalosporina oral introducida recientemente. Su actividad en vitro es similar a cefalexina y cefradina. Su única ventaja sobre las otras cefalosporinas orales es que las concentraciones séricas y en orina son más sostenidas lo cual le permite que su administración sea menos frecuente (41, 43). Estudios clínicos demostraron que un gramo dos veces al día de cefadroxil es igualmente efectivo que 500mg cuatro veces al día de cefalexina para infecciones urinarias (44, 45).

Cefalosporinas Parenterales

Cefazolina

La actividad en vitro es similar a la de cefalotina en contra de micro-organismos gram-positivos como lo son el pneumococo, los estafilococos, y los estreptococos (8). Es igualmente activa que la cefalotina en contra de *Proteus mirabilis* y *Klebsiella pneumoniae*, y más activa en contra de *Escherichia Coli* (53). Su ventaja sobre las otras cefalosporinas de la primera generación es que se obtienen concentraciones séricas más altas y la relativa ausencia de dolor después de administración intramuscular (8). Se recomienda 500mg a un gramo cada seis a ocho horas intramuscular para infecciones menores y para infecciones severas hasta un máximo de 12gramos al día por vía endovenosa.

Cefoxitina

Cefoxitina es un derivado semi-sin-

tético de cefamicina C (9). El grupo metoxy en la posición 7 del anillo beta lactámico le confiere mayor resistencia a las beta lactamasas de los bacilos gram-negativos (6). Es menos activa que las otras cefalosporinas en contra de los estafilococos y estreptococos (9). Tiene igual o mayor actividad que las otras cefalosporinas en contra de *E. coli*, *Klebsiella pneumoniae* y *Proteus mirabilis* (29). La resistencia de este agente a la degradación por beta lactamasas la hace activa en contra de *Serratia*, *Proteus* índole positivo, *Providencia* y *Citrobacter*; no es muy activa en contra de *Enterobacter* (29). A las dosis recomendadas inhibe un 83 por ciento de las cepas de *Bacteroides fragilis* (31). Es activa en contra de *Neisseriae gonorrhoeae* inclusive las cepas que producen penicilinasas (39). Al igual que las cefalosporinas no tiene actividad en contra de *Pseudomonas aeruginosa* (29). Farmacológicamente es bastante similar a las otras cefalosporinas; se recomienda una dosis de 1-2 gramos cada 4-6 horas por vía endovenosa.

Cefamandole

Cefamandole tiene una actividad in vitro en contra de cocos gram-positivos similar a cefalotina (54). Es activa en contra de *E. coli*, *Klebsiella pneumoniae*, *Citrobacter* y *Providencia* resistentes a las cefalosporinas de la primera generación; no es muy activa en contra de *Serratia* (27, 54). Es la única cefalosporina parenteral que demuestra actividad en contra de *Haemophilus influenzae* (32). No demuestra actividad significativa en contra de *Bacteroides fragilis* y *Pseudomonas aeruginosas* (27, 31). Su farmacología es similar a las otras cefalosporinas y se recomienda en dosis de 1-2 gramos cada 6-8 horas; hasta un máximo de 12 gramos por día.

Moxalactam y Cefotaxime

Moxalactam (Ly 127935) y cefotaxime (HR756) son dos antibióticos beta lactámicos, relacionados a las cefalosporinas, que se encuentran bajo investigación (13, 14). Han demostrado una actividad *in vitro* excelente en contra de micro-organismos gram-positivos y bacilos gram-negativos a concentraciones bien bajas. Son estables a las beta lactamasas y tienen actividad en contra de bacilos gram-negativos resistentes a gentamicina y en contra de los anaeróbicos específicamente *Bacteroides fragilis* (55, 56). Son las primeras cefalosporinas con actividad en contra de *Pseudomonas aeruginosa* (13, 14, 55, 56). Si demuestran la misma actividad en estudios clínicos que han demostrado en estudio *in vitro* serán un arma fuerte en el armamentario del médico en su batalla en contra de las infecciones adquiridas en el hospital.

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ISONIAZID (INH) CYSTITIS

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Resumen: Un varón de 20 años de edad desarrolló cistitis hemorrágica severa después del tratamiento profiláctico con isoniazida.

Se hicieron varios estudios incluyendo cistoscopia, pielografía y evaluación microbiológica. Estos fueron de poca ayuda en el diagnóstico etiológico. Los hallazgos subjetivos y objetivos mejoraron al discontinuar la isoniazida.

Para caracterizar el metabolito específico de la isoniazida (acetilados, hidrolizados, hidrazonados) con propiedades inflamatorias locales, se hicieron varias maniobras farmacológicas. Los resultados sugieren que los productos hidrazonados fueron los mediadores de la inflamación.

Summary: Severe hemorrhagic cystitis followed the prophylactic coverage of INH in a twenty-year-old male, slow acetylator with recent PPD conversion.

Extensive microbiological work-up, intravenous pyelogram and cystoscopic examination, failed to disclose the etiology. Symp-

tomatic and laboratory recovery followed the INH discontinuation.

To further specify the INH metabolite (acetylated, hydrazones, hydrolyzed, INH) carrying the local inflammatory property, the following pharmacologic maneuvers were performed. Isoniazid and acetylisoniazid were administered by mouth and sterile solutions of urine containing INH metabolic products and 0.1 mg percent isoniazid in normal saline were introduced to the bladder. Oral INH and bladder irrigation with urine containing metabolic INH products, reproduced the syndrome. Oral acetylisoniazid and bladder irrigation with INH solution did not reproduce it.

The above suggests that the "hydrazone products" were the inflammatory mediators.

Isoniazid (INH) Cystitis

Certain chemical substances and metabolic products of different organic or inorganic agents are some of the well-known etiologic factors of "non bacterial" lower urinary tract inflammation, the so-called "chemical cystitis" (1).

A case report of INH-induced cystitis follows, which, to the best of our knowledge, has never been previously reported. The patient was a twenty-year-old white male, who was found to have a positive PPD during a routine examination and subsequently was

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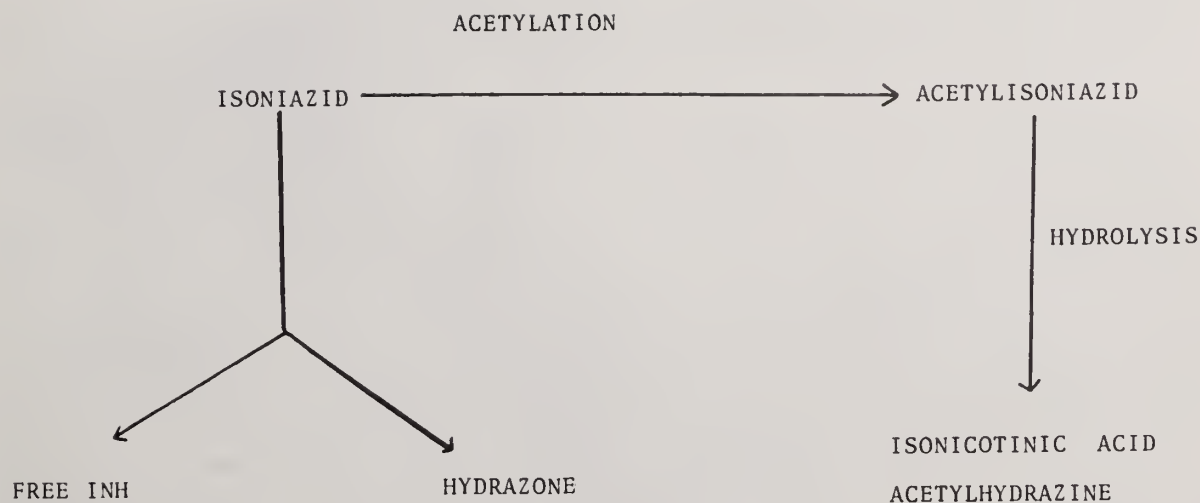


FIGURE 1: INH METABOLISM

started on INH prophylaxis.

Meticulous personal and family history failed to reveal any potential source of tuberculosis exposure. Physical examination was normal. Chest X-ray, CBC, SMA-12 and U/A were also normal. Upon completion of the above tests, the patient was put on 300mg of INH daily. Twenty-four hours later, the patient returned complaining of dysuria, frequency, slight discoloration and mild constitutional symptoms including generalized malaise, nausea and vomiting. The physical examination revealed a mildly distressed individual with normal vital signs; in addition, the suprapubic area was tender to palpitation.

Repeated urinalysis showed many RBC's and epithelial cells. CBC was normal. Urine cultures, including culture for ureoplasma urealytium and T-mycoplasma, were negative. Because of this unexplained and persistent symptomatology, IVP and urine cultures for TB were done and were normal. INH was then discontinued and the above symptomatology

disappeared in less than twenty-four hours with urine sediment normalization in seventy-two hours.

A challenge dose of INH was given with the same subjective and objective results. Cystoscopy, performed during this period, disclosed diffuse inflammation of the bladder mucosa. Urine specimen was obtained during this procedure, and was refrigerated aseptically.

Cystitis

When INH was discontinued, recovery was again easily accomplished.

To further specify the group of INH metabolites (acetylated, hydrolyzed, hydrazones, INH) the responsible for the local bladder inflammatory properties, the following pharmacologic manipulations were carried out, with the patient's consent. The acetylator phenotype was determined by the ratio of acetylisoniazid to isoniazid in the urine, method described by

S. Kailasam et al (2). The ratio was less than five, and the patient was characterized as slow acetylator.

A single dose of 300 mg acetylisoniazid was administered by mouth to the patient, and his urine was examined microscopically at four-hour intervals for two days. No evidence of any celluria or appearance of any pathologic element was found, nor the patient became symptomatic. Six days later, the refrigerated sterile urine specimen containing INH metabolic products, properly diluted (1:5) in sterile solution of normal saline, was introduced to the bladder through a Foley catheter. The Foley catheter was removed immediately and the urine was examined microscopically at four-hour intervals for two days. The first specimen contained 100-200 red blood cells per cu, and the second was grossly hemorrhagic. The patient complained of dysuria also. Thereafter the symptomatology improved in 24 hours and the urine returned to normal in five days. Six days later, a sterile saturated solution of 0.1 mg percent INH in normal saline was introduced to the bladder, in a similar to above way, and the urine was examined microscopically at four-hour intervals for two days. No evidence of microscopic hematuria or symptomatic dysuria occurred.

Discussion

Isoniazid is metabolized primarily by acetylation to acetylisoniazide, at a rate depending on the acetylator phenotype. In slow acetylators, INH is excreted 63 percent as acetylisoniazid and its hydrolyzed metabolites (isonicotinic acid, acetylhydrazine) and 37

percent as either free isoniazid or isoniazid hydrazone. On the contrary, in the fast acetylators 94 percent is excreted as acetylisoniazide and its metabolites and only 3.6 percent as free isoniazid and its hydrazone products (3).

The introduction and reproduction of the inflammatory cystitis, by the oral administration of INH, and bladder irrigation with urine containing INH metabolites, on the one hand, and the inability of acetylisoniazide to produce the above syndrome, on the other hand, leads to two conclusions. First INH metabolites had the inflammatory properties and second the acetylation and its hydrolyzed products were irrelevant to the etiologic mechanism. The free excreted INH and its hydrazone products seem to be the responsible etiologic metabolic fraction. The introduction of INH in the bladder, although in concentrations unrealistically higher, did not reproduce cystitis. Phenomenon suggesting that "hydrazone products" were inflammatory mediators.

The slow acetylator phenotype of the patient, resulting in higher excretion and concentration of hydrazone products in the bladder, and in addition, a localized idiosyncratic sensitivity of the bladder mucosa to hydrazones, is the postulated mechanism.

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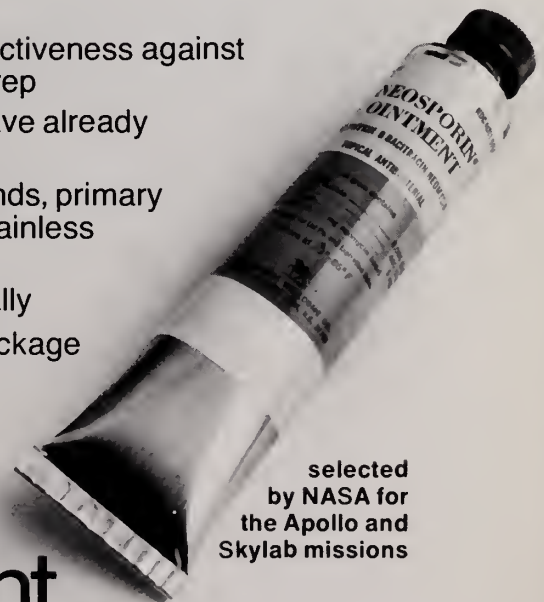
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Each gram contains: Aerosporin® (Polymyxin B Sulfate) 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs, in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations,

prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.



Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

SEPTRA DS

each tablet contains 160 mg trimethoprim
and 800 mg sulfamethoxazole

B.I.D.



THE POWER TO PERFORM IN RECURRENT INFECTIONS OF THE UPPER AND LOWER URINARY TRACT*

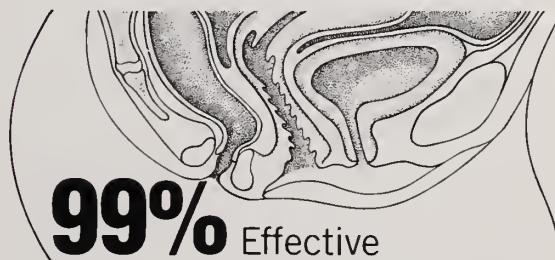
The therapeutic key: high urine levels

Septra achieves high urine levels rapidly, with peak serum levels occurring one to four hours after oral administration.

The therapeutic difference: double blockade plus penetration

The sequential blocking action of bacterial folate metabolism by the component agents in Septra is believed to potentiate the effect of the combination against sensitive bacteria.¹ This double-blockade also discourages the development of bacterial resistance.

In addition, Septra actually penetrates into,[†] and concentrates at, the sites where recurrence in women is usually instigated^{2,3}— bladder, vaginal introitus and bowel mucosa.



The powerful performance of Septra® DS b.i.d.

In the office: Septra demonstrates a high response rate in both recurrent cystitis⁴ and recurrent pyelonephritis.⁴

A study of 59 patients with symptomatic upper urinary tract infection showed that Septra achieved 91.5% bacteriologic cure rate[‡] when evaluated up to seven days post-therapy. Of the 53 patients available for follow-up, 96.2% maintained bacteriologic cure from one to four weeks post-therapy.⁴

In another study of 172 patients, many with recurrent cystitis, Septra achieved a 99.7% bacteriologic cure[‡] at end of therapy; 72.7% cure up to 18 days post-therapy.⁴

In the laboratory: Septra is effective against susceptible strains of *E. coli*, *Klebsiella-Enterobacter* and *Proteus*.[§]

PRESCRIBING CONSIDERATIONS: Septra is contraindicated during pregnancy and the nursing period, in patients hypersensitive to its components, and in infants under 2 months. During therapy maintain adequate fluid intake, perform frequent CBCs and urinalyses with microscopic examination.

*due to susceptible organisms

†tissue levels do not necessarily correspond to clinical effectiveness

‡10,000 or fewer organisms/ml urine

§*in vitro* data do not necessarily correlate with clinical results.

SEPTRA® DS

each tablet contains: 160 mg trimethoprim
and 800 mg sulfamethoxazole

The power to perform in recurrent infections of the upper and lower urinary tract.*

*due to susceptible organisms

SEPTRA DS

Double Strength

Each tablet contains: 160 mg trimethoprim† and 800 mg sulfamethoxazole

INDICATIONS AND USAGE:

URINARY TRACT INFECTIONS: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

NOTE: Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of these urinary tract infections.

ACUTE OTITIS MEDIA: For the treatment of acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in the judgment of the physician, Septra offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septra when the infection is due to *Haemophilus influenzae* resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS: For the treatment of acute exacerbations of chronic bronchitis due to susceptible strains of *Haemophilus influenzae* and *Streptococcus pneumoniae* when in the judgment of the physician, Septra offers some advantage over the use of a single antimicrobial agent.

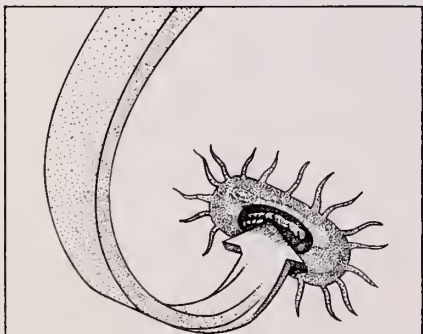
SHIGELLOSIS: For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

PNEUMOCYSTIS CARINII PNEUMONITIS: Septra is also indicated in the treatment of documented *Pneumocystis carinii* pneumonia. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period (see "Reproduction Studies"). Infants less than two months of age.

WARNINGS: SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A, β -hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.



Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but it has been reported to interfere with hematopoiesis in occasional patients. In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombopenia with purpura has been reported.

The presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. Complete blood counts should be done frequently in patients receiving Septra. If a significant reduction in the count of any formed blood element is noted, Septra should be discontinued.

PRECAUTIONS: Septra should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

It has been reported that Septra may prolong the prothrombin time of patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when Septra is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

ADVERSE REACTIONS: For completeness, all major reactions to sulfonamides and to trimethoprim are included below even though they may not have been reported with Septra.

Blood Dyscrasias: Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia.

Allergic Reactions: Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis.

Gastrointestinal Reactions: Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis.

C.N.S. Reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness.

Miscellaneous Reactions: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L.E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Goiter production, diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, ACUTE OTITIS MEDIA IN CHILDREN AND ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS.

Adults: The usual adult dosage for the treatment of urinary tract infections and acute exacerbations of chronic bronchitis is one Septra DS Tablet every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. In children weighing 88 lbs (40 kg) or more, the dosage is one Septra DS Tablet every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15-30	Half of the usual dosage regimen
Below 15	Use Not Recommended

PNEUMOCYSTIS CARINII PNEUMONITIS:

The recommended dosage for patients with documented *Pneumocystis carinii* pneumonia is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. In children weighing 70 lbs (32 kg) or more, the dosage is one Septra DS Tablet every 6 hours for 14 days.

HOW SUPPLIED: Oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole — bottle of 100, unit dose pack of 100 and COMPLIANCE™ Pak of 20.

Also available in regular tablets containing 80 mg trimethoprim and 400 mg sulfamethoxazole (bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100) and oral suspension containing 40 mg trimethoprim and 200 mg sulfamethoxazole in each 5 ml (bottle of 473 ml. Unit of Use: bottle of 100 ml with child-resistant cap).

Reproduction Studies: In rats, doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palate. The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In rabbits, trimethoprim administered by intubation from days 8 to 16 of pregnancy at dosages up to 500 mg/kg resulted in higher incidences of dead and resorbed fetuses, particularly at 500 mg/kg. However, there were no significant drug-related teratological effects.

REFERENCES: 1. Kucers A, Bennett N Mck: *The Use of Antibiotics: A Comprehensive Review with Clinical Emphasis*, ed 3. Philadelphia, Lippincott, 1979, p 700. 2. Stamey TA, Condy M: The diffusion and concentration of trimethoprim in human vaginal fluid in *Trimethoprim/Sulfamethoxazole: A Compilation of Clinical and Pharmacodynamic Studies in Chronic and Recurrent Urinary Tract Infection*. New York, Science & Medicine, 1975, p. 13. 3. Naff H: On the changes in the intestinal flora induced in man by Bactrim®. *Path Microbiol* 37: 1, 1971. 4. Data on file, Burroughs Wellcome Co.

†Mfd. under Pat. #3,956,327



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SEXUALLY TRANSMITTED DISEASES

PART II

SYPHILIS, CHLAMYDIAS, HERPES AND SCABIES

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Syphilis

The clinical manifestations of syphilis have been reviewed extensively and there are few developments that are not found in standard textbooks (1, 2).

We will address ourselves specifically to developments in the field and to emphasize treatment.

The following represent some of the major recent developments concerning syphilis (3, 4). 1) Up to now, attempts to culture *Treponema pallidum* on an artificially defined medium have been unsuccessful. 2) A new serological test using treponemal antigen has been developed and promises to replace the fluorescent treponema antibody absorption test (FTA-ABS) because of its simplicity, potential quantification and the possibility that it may be performed by automated procedures. The test is called the micro-hemagglutination

test (MHA-TP) for *T. pallidum*. It is less sensitive than the FTA-ABS in primary syphilis but should have the same specificity since it uses treponemal antigen which has been attached to erythrocytes. 3) The percentage of men contracting syphilis who are homosexual or bisexual is increasing and may approach 40 percent of the total male cases in some areas. 4) The most consistently successful method of containing the spread of syphilis is the adequate treatment of the patient and his/her sexual contacts. This necessitates reporting the case to the Public Health Department and epidemiological investigation. The patient should be assured that confidentiality will be maintained. 5) From the standpoint of therapy simplifications have been made (5, 6). Syphilis is either defined as being less than one year, more than one year, or indeterminate in duration. Syphilis of less than one year's duration can be treated with 2.4 million units of benzathine penicillin or alternately 30 grams of tetracycline or erythromycin given over a fifteen-day interval. When syphilis is of more than one year's duration or of indeterminate duration and neurosyphilis is not present, the patient can be treated with 2.4 million units of benzathine penicillin once a week for three weeks or for 30 days with either tetracycline or erythromycin at a daily dosage level of two grams. Since benzathine

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penicillin does not cross into the cerebrospinal fluid, it is necessary to know if neurosyphilis is present. This necessitates performance of a lumbar puncture. If asymptomatic or active neurosyphilis is diagnosed, a different penicillin regimen is necessary. In active neurosyphilis, many experienced clinicians advocate hospitalization and therapy with high-dose penicillin (20 million units per day for ten days). Adequate follow-up of patients with active neurosyphilis is essential. It is not necessary to perform a lumbar puncture in patients with syphilis of less than one year in duration since it has been demonstrated that appropriate therapy at this stage prevents the occurrence of neurosyphilis.

The optimal treatment schedules for syphilis of more than one year's duration have been less well established than schedules for early syphilis. In general, syphilis of longer duration requires higher-dose therapy. Although therapy is recommended for established cardiovascular syphilis, there is little evidence that antibiotics reverse the pathology associated with this disease.

Cerebrospinal fluid (CSF) examination is mandatory in patients with suspected, symptomatic neurosyphilis. This examination is also desirable in other patients with syphilis of more than one year's duration to exclude asymptomatic neurosyphilis.

Published studies (6,7) show that a total dose of 6.0-9.0 million units of penicillin G results in a satisfactory clinical response in approximately 90 percent of patients with neurosyphilis. There is more published clinical experience with short-acting penicillin preparations than with benzathine penicillin G (6,7). Some clinicians prefer to hospitalize patients with neurosyphilis, particularly if the patient is symptomatic or has not responded to initial therapy. In these instances they treat patients with 12-24 million units of aqueous crystalline

penicillin G given intravenously each day (2-4 million units every 4 hours) for 10 days.

Syphilis in pregnancy should be treated with benzathine penicillin or erythromycin at a dosage level consistent with the duration of disease.

Treatment:

Specific USPHS recommendations for the treatment of syphilis are as follows (7):

Early Syphilis

Early syphilis (primary, secondary, latent syphilis of less than one year's duration)

Rx: (1) Benzathine penicillin G - 2.4 million units total by intramuscular injection.

Benzathine penicillin G is the drug of choice, because it provides effective treatment in a single visit.

or

(2) Aqueous procaine penicillin G - 4.8 million units total: 600,000 units by intramuscular injection daily for eight days.

or

(3) Procaine penicillin G in oil with 2 percent aluminum monostearate (PAM) - 4.8 million units total by intramuscular injection: 2-4 million units at first visit, and 1.2 million units at each of two subsequent visits three days apart.

Although PAM is used in other countries, it is no longer available in the United States.

Patients who are allergic to penicillin:

Rx: (1) Tetracycline hydrochloride - 500 mg four times a day by mouth for 15 days.

or

(2) Erythromycin (stearate, ethylsuccinate or base) 500 mg four times a day by mouth for 15 days.

These antibiotics appear to be effective, but have been evaluated less extensively than penicillin.

Syphilis of more than one year's duration

Syphilis of more than one year's duration (latent syphilis of indeterminate or more than one year's duration, cardiovascular, late benign, neurosyphilis)

Rx: (1) Benzathine penicillin G - 7.2 million units total: 2-4 million units by intramuscular injection weekly for three successive weeks.

or

(2) Aqueous procaine penicillin G - 9.0 million units total: 600,000 units by intramuscular injection daily for fifteen days.

Patients who are allergic to penicillin:

Rx: (1) Tetracycline hydrochloride - 500 mg four times a day by mouth for 30 days.

or

(2) Erythromycin (stearate, ethylsuccinate or base) - 500 mg four times a day by mouth for 30 days.

There are NO published clinical data which adequately document the efficacy of drugs other than penicillin for syphilis of more than one year's duration. CSF examination is highly recommended before therapy with these regimens.

Syphilis in Pregnancy

Evaluation of pregnant women:

All pregnant women should have a non-treponemal serologic test for syphilis, such as the VDRL or RPR tests, at the time of the first prenatal visit. The treponemal tests such as the FTA-ABS test should not be used for routine screening. In women suspected of being at high risk for syphilis, a second non-treponemal test should be performed during the third trimester.

Seroactive patients should be expeditiously evaluated. This evaluation should include a history and physical examination, as well as a quantitative non-treponemal test and a confirmatory treponemal test.

If the FTA-ABS test is nonreactive and there is no clinical evidence of syphilis, treatment may be withheld. Both the quantitative non-treponemal test and the confirmatory test should be repeated within four weeks. If there is clinical or serologic eviden-

ce of syphilis or if the diagnosis of syphilis cannot be excluded with reasonable certainty, the patient should be treated as outlined below.

Patients for whom there is documentation of adequate treatment for syphilis in the past need not be retreated unless there is clinical or serological evidence of reinfection such as darkfield-positive lesions or a fourfold titer rise of a quantitative non-treponemal test.

- Rx: (1) For patients at all stages of pregnancy who are not allergic to penicillin. Penicillin in dosage schedules appropriate for the stage of syphilis as recommended for the treatment of non-treponemal pregnant patients.
- (2) For patients of all stages of pregnancy who are allergic to penicillin. Erythromycin (stearate, ethylsuccinate or base) in dosage schedules appropriate for the stage of syphilis, as recommended for the treatment of non-pregnant patients. Although these erythromycin schedules appear safe for mother and fetus, their efficacy is not well established. Therefore, the documentation of penicillin allergy is particularly important before treating a pregnant woman with erythromycin.

Erythromycin estolate and tetracycline are not recommended for syphilitic infections in pregnant women because of potential adverse effects on mother and fetus.

Follow up

Pregnant women who have been treated for syphilis should have monthly quantitative non-treponemal serologic tests for the remainder of the current pregnancy. Women who show a fourfold rise in titer should be treated. After delivery, follow-up is as outlined for non-pregnant patients.

Congenital Syphilis

Congenital syphilis may occur if the mother has syphilis during pregnancy. If the mother has received adequate penicillin treatment during pregnancy, the risk to the infant is minimal. However, all infants should be examined carefully at birth and at frequent intervals thereafter until non-treponemal serologic tests are negative.

Infected infants are frequently asymptomatic at birth and may be seronegative if the maternal infection occurred late in gestation. Infants should be treated at birth if maternal treatment was inadequate, unknown, with drugs other than penicillin, or if adequate follow-up of the infant cannot be ensured. Infants with congenital syphilis should have a CSF examination before treatment.

Infants with abnormal CSF:

- Rx: (1) Aqueous crystalline penicillin G, 50,000 units/kg intramuscularly or intravenously daily in two divided doses for a minimum of ten days.

or

- (2) Aqueous procaine G. 50,000 units/kg intramuscularly daily

TABLE I
Antichlamydial Antibodies in Selected Populations
Tested at the Hooper Foundation (6,8)

	CF > 1:16 –(°/o)	Micro-IF >1:8 –(°/o)
<i>Screening studies</i>		
<i>Normal adults, all ages</i>	2-3	25-45
<i>Pediatric sera</i>	< 1	10
<i>Trachoma-endemic population</i>	5-15	> 80
<i>Males, venereal disease study, young adults</i>		
<i>without disease</i>	5-10	20-25
<i>Males, syptomatic attending VD clinic</i>	10	60
<i>Females, venereal disease study, young adults</i>	15-20	50-70
<i>Prostitutes</i>	30-60	Up to 85
<i>Proven chlamydial infections (isolation)</i>		
<i>Lymphogranuloma venereum</i>	100	100
<i>Psittacosis</i>	100	ND*
<i>Adult inclusion conjunctivitis</i>	50	100
<i>Male, urethritis</i>	15	90
<i>Female, cervical infection</i>	45	99

* - Not determined

for a minimum of ten days.

Infants with normal CSF:

Rx: Benzathine penicillin G.
50,000 units/kg intramuscu-
larly in a single dose.

Although benzathine penicillin has been previously recommended and widely used, published clinical data on its efficacy in conge-

nital neurosyphilis are lacking. If neurosyphilis cannot be excluded, the procaine or aqueous penicillin regimens are recommended. Since cerebrospinal fluid concentrations of penicillin achieved after benzathine penicillin are minimal to nonexistent, these reviewed recommendations seem more conservative and appropriate until clinical data on the efficacy of benzathine penicillin can be accumulated. Other antibiotics are not recommended for neonatal congenital syphilis.

Penicillin therapy for congenital syphilis after the neonatal period should be with the same dosages used for neonatal congenital syphilis. For older children, the total dose of penicillin need not exceed the dosage used in adult syphilis of more than one year's duration. After the neonatal period, the dosage of erythromycin and tetracycline for congenital syphilitics who are allergic to penicillin should be individualized but need not exceed dosages used in adult syphilis of more than one year's duration. Tetracycline should not be given to children less than 8 years of age.

Follow Up and Treatment

All patients with early syphilis and congenital syphilis should be encouraged to return for repeat quantitative non-treponemal tests 3, 6, and 12 months after treatment. Patients with syphilis of more than one year's duration should also have a repeat serologic test 24 months after treatment. Careful follow-up serologic testing is particularly important in patients treated with antibiotics other than penicillin. Examination of CSF should be planned as part of the last follow up visit after treatment with alternative antibiotics.

All patients with neurosyphilis must be carefully followed with serologic testing for at least three years. In addition, follow-up of these patients should include clinical re-evaluation at 6-month intervals and repeat CSF examinations, particularly in patients treated with alternative antibiotics.

The possibility of reinfection should always be considered when re-treating patients with early syphilis. A CSF examination should be performed before re-treatment unless reinfection and a diagnosis of early syphilis can be established.

Re-treatment should be considered when:

- (1) Clinical signs or symptoms of syphilis persist or recur;
- (2) There is a sustained fourfold increase in the titer of a non-treponemal test;
- (3) An initially high-titer non-treponemal test fails to decrease fourfold within a year.

Patients should be re-treated with the schedules recommended for syphilis of more than one year's duration. In general, only one re-treatment course is indicated because patients may maintain stable, low titers of non-treponemal tests or have irreversible anatomical damage.

Epidemiologic Treatment

Patients who have been exposed to infectious syphilis within the preceding three months and other patients who on epidemiologic grounds are at high risk for syphilis should be treated as for early syphilis. Every effort should be made to establish a diagnosis in these cases.

Chlamydia Trachomatis

The organism:

Chlamydia are obligate intracellular parasites that have been divided into two groups, *Chlamydia psittaci* and *Chlamydia trachomatis*, on the basis of sensitivity to sulfonamides and the ability to form iodine-staining intracyto-

TABLE II

Distribution of Chlamydial CF Titers in Patients with Proven Infections (8)

Disease	No. Tested	No. with CF Titer				
		$\leq 1:16$	1:16	1:32	1:64	$\geq 1:128$
<i>Lymphogranuloma venereum</i>	15	0	1	2	0	12
<i>Psittacosis</i>	30	0	2	5	5	18
<i>Adult Inclusion</i>						
<i>Conjunctivitis</i>	93	46	28	11	6	2
<i>Cervicitis, females</i>	55	30	9	6	4	6
<i>Urethritis, males</i>	60	51	8	1	0	0

plasmic inclusions. *C. trachomatis* is sensitive to sulfonamides and produces inclusions which can be stained by iodine and will be the only group of micro-organisms reviewed in this section. *C. psittaci* is the cause of psittacosis. Both groups of micro-organisms have a common complement fixation test antigen. The particle capable of transmitting infection is called the elementary body. It is endocytosed by columnar epithelial cells and begins to change within the endocytes vesicle into the reticulate or intermediate body. The reticulate body is capable of multiplication by binary fission and, as a consequence of multiple divisions within the vesicle, an inclusion body is formed. Late in the division cycle, elementary bodies are again formed. The inclusion body can be stained with iodine, Giemsa stain or fluorescent antibody. When the inclusion body reaches a certain stage of development, lysis occur releasing elementary bodies to initiate another cycle of infection. Chlamydial infections are noted for their persistence and for their capacity to become latent. Chlamydia can be

demonstrated by direct staining of the inclusion body in cells or they can be cultured in the yolk sac of embryonated chicken eggs or in tissue culture (8). It has been determined that prior irradiation of the tissue culture cells or pre-treatment with idoxuridine increases the size of the intracytoplasmic inclusion and decreases the capacity of cells to divide thus making the inclusions easier to demonstrate. McCoy cells and certain strains of HeLa cells have been found to be sensitive means for isolation of the chlamydia and tissue culture constitutes the most effective means of demonstrating the micro-organisms.

C. trachomatis can be divided into serotypes by the micro-immunofluorescent method of Wang and Gryston (10). Serotypes A through C are the cause of endemic trachoma; D through K cause oculogenital infections and L₁, L₂ and L₃ are the serotypes causing LGV.

Non specific urethritis and epididymitis:

One of the most common sexually

transmitted diseases in the world today is non-specific urethritis (11, 13). Symptoms include dysuria and urethral discharge, but that discharge is mucopurulent and generally not frankly purulent as in gonorrhea. A smear taken from within the urethra reveals at least five leucocytes per high-power field and the absence of intracellular gram-negative diplococci. Usually *C. trachomatis* causes anterior urethritis but is capable of invading the posterior urethra where it can cause epididymitis (14, 12). In males below the age of 35 years, *C. trachomatis*, serotypes, D-K, have been shown to be a definite cause of epididymitis (6, 16).

Ureaplasma urealyticum, a strain of mycoplasma producing small (T) colonies and able to split urea, probably constitutes the cause of approximately 30 percent of the cases of non-specific urethritis (28, 29). Although *Trichomonas vaginalis* and herpes simplex virus can rarely cause non-specific urethritis, the remaining causes of about 30 percent of the cases do not have a known etiology at the present time.

Conjunctivitis:

Follicular conjunctivitis with inclusion bodies can occur in sexually active adults (21). The conjunctivitis is characterized by the presence of follicles (collection of mononuclear cells) on the conjunctival surfaces and for its chronicity. Pannus formation, consisting of neovascularization and corneal scarring, and which is characteristic of trachoma usually does not occur in these infections. It is to be noted that pannus formation in endemic trachoma areas usually occurs with the second or third infection. In experimental infections with non-humans primates, pannus formation occurs only with repeated infections. Thus, one thesis of the pathogenesis of trachoma

is that it occurs from repeated infections with the same or different serotypes often in a family setting, and where the predominant mode of transmission is eye-finger-eye.

Chlamydias and the Female:

In the female, asymptomatic carriage in the endocervix may occur as well as mucopurulent cervicitis. In the latter condition the cervix becomes edematous resulting in the endocervix becoming apparent to external observation (ectropion) (23, 24). Mucopus can be seen extending through the os. The micro-organism is also capable of ascending into the endosalpinx and it has been shown in Scandinavia that *C. trachomatis* can cause PID. The micro-organism in females also is capable of ascending into the urethra and it is a prime candidate for a potential role as a cause of the urethral syndrome (dysuria, frequency, negative bacterial cultures with or without pyuria). Antibody studies illustrate the prevalence of chlamydia infections and indicate that low-level complement fixation antibody titers with the group specific antigen are common with urethral endocervical and conjunctival infections. See Tables I, II. (6, 8)

Chlamydias and the neonate:

The neonate is an important cause of concern. An infant born to a mother with endocervical carriage of *C. trachomatis* may develop neonatal inclusion body conjunctivitis (25). The incubation period is 7-12 days and differs from the 2-3 day incubation period of gonococcal ophthalmia neonatorum. The course is chronic and parents of the affected child may have or develop non-specific urethritis, conjunctivitis or PID. A new disease syndrome has recently been described by Beem and Saxon (26). They found that *C. trachomatis* was the cause of a distinctive

form of pneumonia in children. The onset of the pneumonia was gradual and generally began at 1-3 months of life. It was characterized by a staccato cough, interstitial infiltrates, eosinophilia, and a tendency to chronicity. *C. trachomatis* can be grown from the nasopharynx, trachea and conjunctivae of these infants. The infant may come into contact with both micro-organisms by aspiration of cervical mucus during the delivery process (26).

Management:

Therapy of urethritis and mucopurulent cervicitis due to *C. trachomatis* consists of two grams of tetracycline for 7-10 days (27). Erythromycin at the same dosage level is an alternate therapeutic regimen. *C. trachomatis* is the cause of more than 40 percent of the non-specific urethritis seen. This includes 70 percent of post-gonococcal urethritis. Since non-specific urethritis may be caused by other agents (28, 29), it has been debated whether the female contact of the male with non-specific urethritis should be treated. Since the micro-organism can produce mucopurulent cervicitis and PID and can be transmitted to the infant, it is recommended at the present time that sexual contacts secure epidemiological treatment in a similar manner as with gonorrhea. (6)

Lymphogranuloma venereum (LGV):

Lymphogranuloma venereum is one of the traditional venereal diseases and can be considered to represent the generalized form of chlamydial genital infections similar to disseminated gonococcal infection (DGI) in gonorrhea (30, 31). LGV is characterized by a painless evanescent papule appearing 3-5 weeks after the

time of inoculation. The papule last 3-4 days and the patient rarely seeks medical attention because of its presence. Inguinal lymphadenopathy then follows. The adenopathy can be bilateral or predominantly unilateral, involving both the femoral and the inguinal lymph nodes. The characteristic groove sign may be produced in which the inguinal ligament separates enlarged lymph nodes and causes a groove between the nodes. The lymph nodes can suppurate and form buboes. LGV in its acute form can also produce typical clinical manifestations of arthritis, generalized lymphadenopathy, pericarditis, hepatitis, and aseptic meningitis. In homosexual males, anoproctitis can occur with involvement of the colon to the extent that the diagnosis of ulcerative colitis may be made. In homosexual men and in women where inoculation has been on the posterior vaginal wall, one characteristic late complication of the disease is formation of a tubular rectal stricture. The infection is a classic example of persistence: late in its course and hyperglobulinemia may be present. Treatment is with tetracycline for a four-week period of time. The diagnosis of LGV can be made by the complement fixation test, usually requiring a fourfold rise in titer to a dilution of at least 1:128 (30, 31).

Herpes Genitales (HSV)

Introduction:

Genital herpes simplex viral infection is increasing in frequency. It has been determined that in certain sexually transmitted disease (STD) clinics the virus can be recovered by culture from 40 percent of genital ulcers (32,33). During the initial infection, the virus ascends to sacral root ganglion cells where it presumably remains for the lifetime of the individual. Primary infection lasts 3-4 weeks, is accompanied by

painful vesicles and ulcers, and by regional lymphadenopathy. Occasionally during the primary infection, aseptic meningitis may result. A peripheral neuropathy corresponding to involvement of the nerves in the caudae equina has also been described. In a rare patient, generalization of the virus has occurred with hepatic dysfunction and, ultimately, death. The patient may be subjected to recurrent infection, which generally lasts about 7-10 days with the episodes usually tending to become less frequent with time (6, 35).

Management:

There is proven therapeutic modality effective at present in ameliorating the disease process. The critical question to be answered is why so much difficulty is encountered in the therapy of genital herpes when effective agents have been found to treat herpetic keratitis, vis., ointments containing idoxuridine, adenine arabinoside, adenine arabinoside monophosphate, and trifluorothymidine. The therapeutic dilemma can be divided into two components: 1) Shortening the duration of the initial or recurrent episodes and 2) preventing recurrent episodes. With regard to shortening the duration of the episode itself, to date, too little attention may have been paid to the pharmaceutical formulation of the drug. The antiviral drug must penetrate the epithelial tissue and its solubility in the tissue must exceed its solubility in the vehicle, i. e., the partition coefficient of the drug in the ointment should favor entrance into the skin. British workers (37) have reported success with idoxuridine in dimethylsulfoxide and this formulation is being tested now by investigators in Seattle (37). A new drug, acyclovir, is presently being tested in the U. S. The drug is selectively changed to its active phosphorylated derivative by the viral-coded

enzyme, thymidine kinase, and accumulates in infected cells where it functions in an antiviral capacity by blocking the action of viral DNA polymerase. This new drug appears to have the greatest promise in shortening the duration of the primary or recurrent episode. It should be noted that in recurrent disease, new vesicles appear over a finite period, sometimes for as long as a period of five days. This may infer continued "firing" of the virus into the area of the lesions from its source in the dorsal root ganglion. If topical therapy is effective in recurrent disease, it seems difficult to imagine that it might prevent further episodes since the virus has already been implanted in the ganglion during the primary infection. A report claiming efficacy of 2-deoxy-D-glucose needs to be watched with caution and should be repeated by other investigators with quantitative virological techniques before any potential clinical application (6,37).

Preventing recurrent episodes appears to be a more difficult problem. To date, most efforts have been directed toward an augmentation of the immune response (inactivated vaccine, BCG vaccine, transfer factor, levamisole, inosiplex). There is no evidence that such therapies are effective and no solid information that patients troubled by frequent recurrences have a demonstrable immunological defect.

HSV and the neonate:

One of the feared complications of genital herpes infection is transmission of the virus to the neonate (36). The case-fatality ratio in this disease has approximated 90 percent in some series. Although obstetricians are cognizant of the problem and perform C-sections in pregnant women with active lesions at delivery, the disease continues to occur, generally in women with inadequate prenatal care and counseling and to women who give

no history of the disease and who have no demonstrable lesions at the time of delivery. It has been possible to culture the virus from the cervix of such women in certain instances after neonatal infection has been recognized and directs attention to its possible source. In a National Institute of Allergy and Infectious Diseases (NIAID) sponsored multi-institutional study, parenterally administered adenine-arabinoside (15 mg/kg/day for 10 days) has been shown to have a significant therapeutic effect on the course of neonatal herpes. Although the effect was significant and in the right direction, it most probably should be considered marginal (37). A new study is planned using adenine arabinoside (25 mg/kg/day for ten days) and acyclovir.

Dealing with the Patients:

In dealing with patients with genital herpes, effective counseling is essential. The diagnosis should be established by culture or a Tzanck preparation (34). Therapeutic limitations should be explained to the patient as well as the fact that present research may eventually yield a successful treatment. The patient should be told that he/she is most infectious when active lesions are present and intercourse should be avoided at that time. If the patient is not sure of his/her infectivity, a condom should be worn. The women should have a Pap smear once a year to detect early dysplastic changes. The couple planning a family should advise their obstetrician of the problem so that necessary precautions can be taken at delivery. Self-help organizations are in existence and can help the patient become more comfortable with his/her disease.

Scabies

Infestations by *Sarcoptes scabiei* result from close human contact and are being in-

creasingly recognized as one of the sexually-transmitted diseases (38, 39). Important investigations into the nature of scabies were undertaken by Mellanby at the beginning of World War II (38). It was expected that scabies would become epidemic during the war. Using conscientious objectors as volunteers, it was found difficult if not impossible to infect them if they wore clothes or slept in the bedding of proven scabetic patients. The female mite, however, could be extracted from the end of the serpiginous burrow created during egg laying and then implanted into the skin of the volunteers. No changes could be noticed for one month when pruritus developed. In primary infections, the number of adult female parasites increased dramatically through 100-150 days when a down-turn in female mite burden occurred spontaneously (38). When the female mite was implanted in persons previously infected but cured of their infection, the total mite burden over the same period of time was dramatically reduced. Symptoms, however, began at the onset of infection and often overshadowed those seen with primary infections (6,38). It has been reasoned that the follicular, papular eruption that is widely distributed over areas where mite burrows are absent results from sensitization to the presence of the mite and its products. Secondary infection may occur. If nephritogenic Group A streptococci are present in the population such as in Trinidad, West Indies, scabetic infections may be a major factor predisposing such patients to the development of acute glomerulonephritis. Diagnosis is usually made by the clinical presentation of the patient, with a pruritic rash particularly worse at night in a characteristic distribution and clinical appearance. Some authorities suggest the necessary demonstration of the female mite to sophisticate the clinical impression and avoid over-diagnosis. Treatment is with gamma-benzene

hexachloride ointment (Kwell) applied to the body below the face after a complete bath. After twelve hours of application, the ointment should be removed by another bath. Partners should also be treated; clothes and bedding should be washed. Since many of the symptoms result from sensitization to the parasite and its products, the patient should be instructed not to expect immediate relief. Repeated administration of the ointment should be avoided because of the possible development of skin sensitization to the drug (40).

Other conditions:

We have not presented in detail other conditions such as chancroid caused by *Hemophilus ducreyi* and treated with sulfisoxazole 1.0 gram every six hours for 7-14 days. The diagnosis is based mostly on clinical grounds and a negative dark-field examination. A gram stain may reveal gram-negative coccobacilli in chains or in "school of fish" pattern. Syphilis must be excluded in such cases (31, 41, 42).

We also want to refer our readers to the following references on these specific problems:

1. Sexually-transmitted infections during pregnancy (43).
2. Relationship between STD and urinary tract infection (44).
3. Management of vaginal infection (45).

We have presented a review of the present status on pathogenesis, diagnosis and treatment of common STD. We have not attempted to cover every aspect since there are many other excellent reviews on the sub-

ject. We sincerely hope this review will help all of us that treat STD, in the management of such cases.

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FUTURO Y PERSPECTIVAS DE LAS ENFERMEDADES INFECCIOSAS EN PUERTO RICO

El campo de las enfermedades infecciosas ha estado creciendo a un ritmo nunca visto antes. Si hojeamos las revistas médicas contemporáneas notamos que en todas las ediciones aparecen un número considerable de artículos referentes a procesos infecciosos. Ya se habla de la posibilidad de que ciertas enfermedades del colágeno, y aún más importante, enfermedades malignas sean posiblemente causadas por agentes infecciosos.

Creemos que uno de los eventos más importantes que ayuda e impulsa el futuro desarrollo de la especialidad de las enfermedades infecciosas y la microbiología clínica en nuestra isla es la localización del edificio de Ciencias Médicas dentro de los confines del Centro Médico de Puerto Rico. Este, tan deseoso e importante acontecimiento para las ciencias clínicas, permite potencialmente traer a la cabecera del paciente que padece de un proceso infeccioso al microbiólogo y virólogo e integrarlo al equipo de médicos que tratan de diagnosticar y curar al paciente infectado. Por razones de distancia antes esto no era posible. Exhortamos a estos científicos a que sigan trabajando con nosotros los clínicos para que nos integremos en un equipo eficiente y capaz para diagnosticar y curar al paciente que padece de una infección que amenaza con acabar su vida. Hay que mencionar también dos facilidades médicas las cuales han contribuido decisivamente al desarrollo de la especialidad de las enfermedades infecciosas y la microbiología clínica en nuestra isla; el hospital de Veteranos y el Centro para el Control de Enfermedades Transmisibles del Servicio de Salud Federal cerca del Centro Médico. Ambas instituciones han contribuido al entrenamiento de estudiantes pregraduados y post-graduados y al desarrollo de pruebas de laboratorio para diagnosticar padecimientos infecciosos en nuestra Isla.

Con el establecimiento del Centro Médico de Mayagüez, los hospitales sub-regionales de Arecibo, Bayamón, Caguas, Humacao, y los hospitales de Ponce, Fajardo y otros, ha surgido la necesidad de entrenar especialistas en enfermedades infecciosas. Este nuevo profesional no solo actúa como consultor clínico y maestro si no que también actúa como el Presidente del Comité que trata de controlar las infecciones asociadas a la hospitalización y a la vez es el coordinador clínico con la Sección de bacteriología o microbiología del laboratorio clínico del hospital en donde desempeña sus labores.

Por esta razón se ha fortalecido el programa de entrenamiento en dicha especialidad cual fue originado como programa de entrenamiento formal en el Hospital de Veteranos en el año 1973. Se ha fortalecido el programa integrando los talleres clínicos del Hospital Universitario, Hospital Municipal de San Juan y el Hospital de Veteranos. El entrenamiento en microbiología clínica se efectúa en el Hospital de Veteranos y la experiencia en investigación en el Laboratorio de Enfermedades Infecciosas del Hospital de Veteranos y el Laboratorio de Esquistosomiasis del Hospital Universitario. Este programa contempla entrenar en diez años los infectólogos que se necesitan en Puerto

Rico que estimamos deben de ser un mínimo de veinte y cinco. El entrenamiento en enfermedades infecciosas dura dos años en que el Fellow desarrolla una máxima eficiencia en el diagnóstico y tratamiento de pacientes con procesos infecciosos además de entrenarse en microbiología clínica, farmacología y farmacocinética antimicrobiana, parasitología, epidemiología y control de infecciones e investigaciones en este campo de la medicina. Se utilizan los recursos del Departamento de Microbiología de la Escuela de Medicina de la Universidad de Puerto Rico, los laboratorios clínicos y de investigación del Hospital de Veteranos y los laboratorios de Enfermedades Tropicales y Arbovirus del Centro para el Control de Enfermedades Transmisibles del Servicio de Salud Federal. En un futuro cercano se utilizará el nuevo Centro Latinoamericano de Enfermedades Sexualmente Transmitidas, localizado en el Centro Médico de Puerto Rico. El programa permite desde temprano, exponer a los estudiantes de medicina, internos, residentes y enfermeras a problemas médicos de origen infeccioso que atacan a nuestra comunidad. El programa ha estado muy activo también desarrollando un núcleo de enfermeras epidemiólogas que se dedican a descubrir, estudiar y controlar infecciones hospitalarias.

Al desarrollarse el programa de entrenamiento en enfermedades infecciosas en los últimos años, hemos notado el desarrollo paralelo y muy deseado de la microbiología clínica y ya tenemos localmente desarrollados laboratorios que proveen los medios para inmunoflorescencia diagnóstica, que han automatizado los métodos de cultivos así como también las pruebas de sensibilidades y las concentraciones de antibióticos en suero y orina. Se ha notado también una gran mejoría en los laboratorios de hospitales de la comunidad en el campo de la microbiología clínica.

Al completar su programa de entrenamiento, los infectólogos graduados en el programa se han establecido en la comunidad o se han asociado con los hospitales del Centro Médico y hospitales regionales en Puerto Rico, proveyendo la función de consultores en los aspectos clínicos de las enfermedades infecciosas. Con el núcleo de infectólogos que ahora tenemos hemos podido llevar a cabo un programa de educación médica en nuestra especialidad a través de toda la isla que continuará.

Lo que se ha logrado empezó con las inquietudes de Ashford y sus contemporáneos. Más tarde fue continuado por los doctores Rodríguez-Molina, Oliver-González, Díaz-Rivera, Sotomayor, Ramos-Morales, y varios más. Algunos de nosotros entrenamos fuera de Puerto Rico, pero nuestra inspiración de ser especialistas en enfermedades infecciosas surgió de ese grupo de eminentes infectólogos.

El resurgir de la especialidad ha comenzado y esperamos que la llama continúe encendida con los nuevos infectólogos que se entrenen y continúan entrenando.

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LISTA DE ANUNCIANTES

BOEHRINGER INGELHEIM
Catapres

BURROUGHS WELLCOME
Neosporin Top.
Septra

Mc NEIL PHAR.
Haldol
Parafon Forte
Tolectin
Tylenol w/Codeine

MERRELL-NATIONAL
Tenuate

ROCHE LAB.
Librium
Valium

U.S. ARMY
Recruitment

U.S.V. PHARM.
Hygroton

Tenuate 

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AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

INDICATION: Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.

CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).

WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. **Drug Dependence:** Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. **Use in Pregnancy:** Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. **Use in Children:** Tenuate is not recommended for use in children under 12 years of age.

PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics; therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.

ADVERSE REACTIONS: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System:* Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache, rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic:* Urticaria, rash, ecchymosis, erythema. *Endocrine:* Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System:* Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous:* A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.

DOSEAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg tablet three times daily, one hour before meals, and in the evening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg tablet daily, swallowed whole, in the morning. Tenuate is not recommended for use in children under 12 years of age.

OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine[®]) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976

MERRELL NATIONAL LABORATORIES Inc.
Cayey, Puerto Rico 00633

Direct Medical Inquiries to

MERRELL-NATIONAL LABORATORIES

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References: 1. Citations available on request from Medical Research Department, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M. T., O'Dillon, J. O., and Leyland, H. M. A comprehensive review of diethylpropion hydrochloride. In, *Central Mechanisms of Anorectic Drugs*, S. Garattini and R. Samanin, Ed., New York, Raven Press, 1978, pp. 391-404.

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**Overweight may not always be simple...
complications can develop*.**

Complicated or not...

Tenuate[®] Dospan[®] ^{IV}C **(diethylpropion hydrochloride NF)** **75 mg. controlled-release tablets**

A useful short-term adjunct in an indicated weight loss program.

Overweight patients in certain diagnostic categories often require strict appetite control and a successful program of weight reduction may tend to diminish the incidence or severity of the complications in some patients. Diethylpropion hydrochloride has been reported useful in such patients and while it is not suggested that Tenuate itself in any way reduces the complications of overweight, it may have a useful place as a short-term adjunct in a prescribed dietary regimen. **Tenuate should not be administered to patients with severe hypertension; see additional Warnings and Precautions on the opposite page.**

In uncomplicated overweight.

Many patients, on the other hand, present with excess fat but no disease. While this condition is often termed uncomplicated obesity, complications of both a social and a psychologic nature may be distressingly real for the patients. In these cases, a short-term regimen of Tenuate can help reinforce your dietary counsel during the important early weeks of an indicated weight loss program.

Clinical effectiveness.

The anorectic effectiveness of diethylpropion hydrochloride is well documented. No less than 16 separate double-blind, placebo-controlled studies attest to its usefulness in daily practice.¹ And the unique chemistry of Tenuate provides "...anorectic potency with minimal overt central nervous system or cardiovascular stimulation."² Compared with the amphetamines, diethylpropion has minimal potential for abuse.

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*Studies have shown that obesity is associated with an increased incidence of hypertension, symptomatic heart disease, adult-onset diabetes, and other diseases.

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For prescribing information see opposite page.

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Central Control of
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*The Family of Man™ by Roberto Moretti,
a statuary in crystal symbolizing the broad range of
hypertensive patients eligible for therapy with Catapres.

The Alpha Advantage:

It's for all kinds of hypertensives

- Unlike beta blockers, Catapres® has no contraindications.
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Congestive heart failure	Allergic rhinitis
Ventricular hypertrophy	Hepatic disease
Hyperglycemia	Hyperuricemia
Diabetes mellitus	Gouty arthritis
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Like any antihypertensive, use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

work/play—normal hemodynamic responses to exercise maintained.

love—low incidence of impotence and/or loss of libido:
2.8% in 1,923 patients studied.¹

cardiac output—tends to return to control values during long-term therapy.

blood flow—preserved in kidney.

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Other factors must include:

The drug's effectiveness in a given patient, its side effects, warnings, precautions, tolerance, etc. A rational therapeutic choice depends on a careful assessment of all such factors.

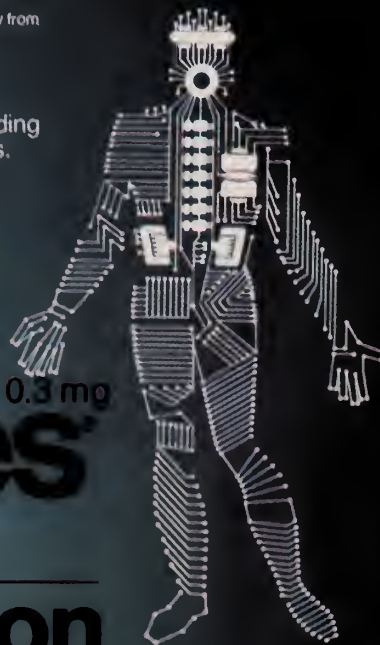
*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

¹ Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

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0.3 mg tablets**

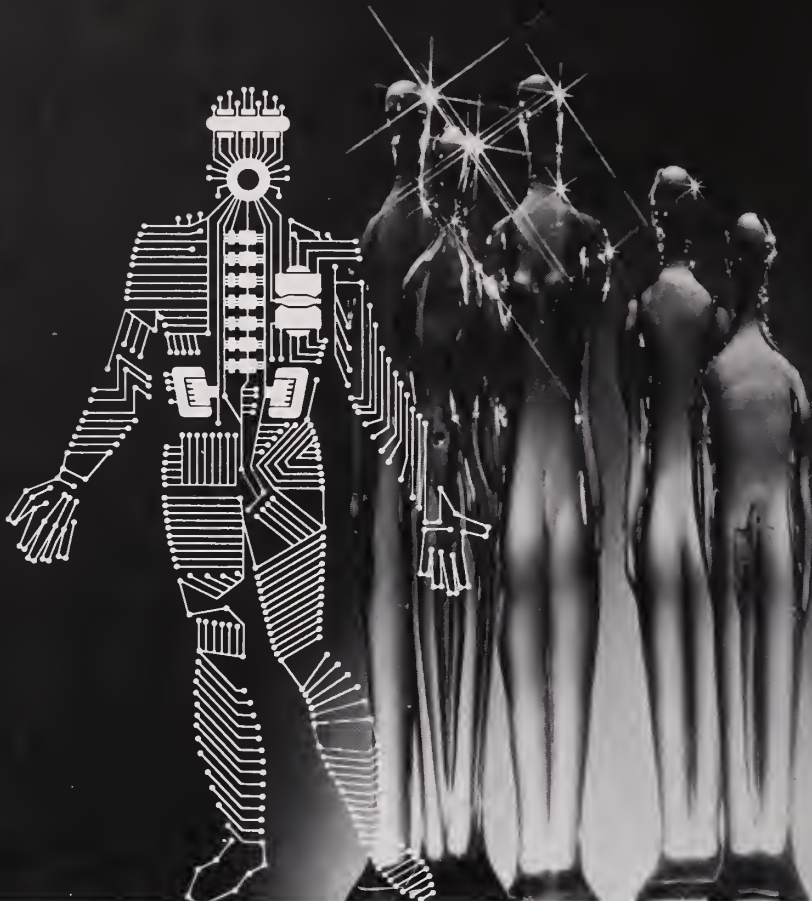
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- No contraindications.
- Effective in all degrees of hypertension. It is mild to moderate in potency.
- Low incidence of depression, impotence, orthostatic hypotension—no fatal hepatotoxicity.
- Preserves kidney blood flow.

Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

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(clonidine hydrochloride)
Tablets of 0.1, 0.2, 0.3 mg

Indication: The drug is indicated in the treatment of hypertension. As an anti-hypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of

The usual starting dose of Catapres is 0.1 mg at breakfast and 0.1 mg at bedtime. Some patients may benefit from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg
Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlor-thalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdose: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) overdose.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000. Also available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

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ANOTHER GREAT DECEIVER INTRAPLEURAL MESOTHELIOMA

S. González Vicente, MD

Dr. Juan M. Aranda
Presidente
Junta Editora
Boletín de la Asociación Médica de P. R.
Box 9387
Santurce, P. R. 00908

Asunto: Trabajo sobre caso de mesotelioma
intrapleural

Estimado doctor Aranda:

Adjunto le envío un caso que sé será de gran interés para vosotros ya que no se ven muchos casos de estos, como usted sabe, y me agradaría que lo publicase en vuestro Boletín.

Favor de dar mis recuerdos a todos mis colegas en ésa y para usted un saludo cordial.

Atentamente

S. González Vicente, MD

ANOTHER GREAT DECEIVER INTRAPLEURAL MESOTHELIOMA

Summary: 0180471-67-M a 76 y/o male caucasian is seen by me with the complaint of difficulty in voiding, epigastric discomfort and tarry stools. Patient was hospitalized for evaluation and treatment and the following findings were observed:

- a) Benign Prostatic Hypertrophy
- b) Epigastric discomfort to deep palpation
- c) Fine crepitances in both bases

A urological consult was obtained and after a negative upper GI series, negative Barium enema, negative chest X-ray, EKG was W.N.L. negative guiac test, U/A was W.N.L., serum lytes normal, normal SMA., and a TUR performed. Pathology report showed an adenofibromatous hyperplasic prostate. Admission date June 2, 1980; discharge date June 18, 1980.

On June 27, 1980 patient came to my office diaphoretic, cold, and pale, with S.O.B. and a tachycardia of 120/min, R-42/m., BP 100/70 (previous BP readings with a mean of 140/82. On physical exam both lung fields showed inspiratory and expiratory wheezes. Pt. was given O₂ by nasal catheter, and aminophyllin 500 mg in D5W 1000 cc drip started, patient transported by ambulance to hospital. During ride to hospital (20 min ride) patient stated he was feeling better and his wheezing had diminished so his tachypnea. His color had improved and things looked better. At this time and due to his condition patient was placed in ICU with a Dx of Pulmonary Embolism. Chest X-ray done stat showed (L) upper and lower pneumonia. Lung Scan was indeterminate. In view of this heparinization was withheld. Patient developed a temperature of 102F and was started on Keflin 1 gm

q.6 hrs piggy back IV. Some improvement was seen but patient remained ill and with S.O.B. On the 29th of June, pt. was done a follow-up Chest X-ray which showed a massive left pleural effusion. Pt. got progressively dyspneic and on auscultation the breath sounds were hardly audible on the left hemithorax. In view of this I decided to proceed with a thoracentesis. A yellowish sero-sanguinous fluid was removed to a total of 2400 cc. This seemed to improve his breathing remarkably. Cell block done on this fluid was negative, and cultures were normal. A surgical consultation was obtained to r/o the possibility of a neoplasm. Bronchoscopy revealed no findings so a diagnostic thoracotomy was performed. Findings revealed an intrapleural mesothelioma (multiple pleural masses). Cytology revealed rapidly mytotic mesothelioma. Pt. is now receiving Adriamycin 30/m2 and Cytosan. Mesotheliomas are uncommon primary

tumors that originate in the cells that line the pleura. A form exists which is very malignant which occurs as tumor masses on both pleuras (parietal and visceral). An abundant exudate is a dead ringer for them and any patient with a massive pleural effusion where there are not other findings should make us think of this type of neoplasm. Some authors claim that it is seen in patients who have been exposed to asbestos inhalation (asbestosis). In this patient there is no history of this.

References

1. Abell, M. R.: Arch Pathol 61: 360-379, 56.
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4. O'Donnell, W. M.: Asbestos and Lung Cancer 19-1143-1148-66.

ANSWERS TO MEDI-QUIZ

1. 0.4 percent
2. d
3. c
4. a
5. d
6. a. T
b. T
c. T
d. T
e. T
7. b
8. c
9. alkalosis, acidosis
10. a. d
b. e
c. a
d. b
e. c

ABSTRACTOS DE LITERATURA MEDICA

BACK AND LEG COMPLAINTS IN RELATION TO MUSCLE STRENGTH IN YOUNG MEN

Karvonen M., Viitasalo J., Komi P., Nummi J., Jarvinen T.: Scand. J. Rehab. Med, Vol 12: pp. 53-59, 1980.

Se realizó un estudio de 183 reclutas con quejas de espalda y piernas, usando un cuestionario y examen médico y relacionando los resultados con antecedentes variables, antropometría, la fuerza isométrica de grupos musculares largos y la resistencia o aguante al correr. Se reportó historial de ciática en 8 por ciento, de lumbago por 13 por ciento, trauma de espalda por 13 por ciento, e insuficiencia de la espalda baja por 63 por ciento. Se asociaron unos extensores del tronco débiles con un historial de ciática; unos flexores de tronco débiles con traumas a la espalda y dolor de espalda con el trabajo o ejercicio. Unos extensores de las piernas débiles demostraron asociación con un historial de insuficiencia de la espalda baja y con ausencias por enfermedad por causa de la espalda y dolor de cadera. Hombres con historial de lumbago y quejas de las piernas y cadera tuvieron un pobre resultado en una carrera de 12 minutos. Las quejas de espalda y piernas fueron más frecuentes en hombres con un status socio-económico alto, con actividad física escasa o que eran obesos. El cuestionario y las medidas de fuerza comprobaron ser adecuados para estudiar el dolor de la espalda baja en sus estadios tempranos.

(Sometido por Miguel A Berríos, MD)

IS EXTRATHORACIC AIRWAY OBSTRUCTION IMPORTANT IN ASTHMA?

Carmen Lisboa, et al., ARRD, 122: 115-121, 1980.

En este artículo importante, los investigadores del grupo del Dr. Peter Macklem de Montreal estudian las curvas de flujo-presión obtenidas en 16 pacientes asmáticos. Sus resultados demostraron que en 7 de estos pacientes la obstrucción principal se localizaba a las aerovías grandes. En estos 7 pacientes, además, los flujos de aire aumentaron más en la fase inspiratoria que en la expiratoria después de los pacientes inhalar mezcla de helio y oxígeno. Este último hallazgo sugiere que el área principal obstructiva era diferente en la fase inspiratoria comparada con la fase expiratoria. Los autores concluyen que en algunos pacientes con asma, la glotis y la traquea extratorácica constituyen áreas que pueden contribuir a la diátesis obstructiva, especialmente en la fase inspiratoria.

(Sometido por Iván León, MD, FCCP)

TREATMENT OF TUBERCULOSIS DURING PREGNANCY

Dixie E. Snider, et al, ARRD: 122: 65-79, 1980

Después de estudiar retrospectivamente 14 mujeres encinta que estaban en quimioterapia en uno de los protocolos de estudio de drogas antituberculosas de la

autora y luego de analizar el desarrollo y desenlace final de casos de mujeres encinta que otros autores han reportado en la literatura, este grupo de investigadores llegan a las siguientes conclusiones y recomendaciones: (1) si la enfermedad tuberculosa pulmonar no es extensa durante el embarazo la combinación de isoniazida con etambutol parece la más segura y apropiada; (2) si una tercera droga se hace necesaria por lo extensa y severa que es la enfermedad, rifampin debe añadirse, (3) el aborto rutinario terapéutico, para una mujer encinta tomando estas drogas de primera línea de tratamiento, no está médicamente indicado.

(Sometido por Iván León, MD, FCCP)

ENFERMEDAD NEUMOCOCCICA DESPUES DE USO DE LA VACUNA NEUMOCOCCICA

Broone, C. V, Facklam, R. R. and Fraser, D. W. *New Engl. J Med.* 303: 549-552, 1980.

La vacuna neumocócica (Pneumovax ®) está indicada para personas de 2 años de edad o más que tienen problemas con el bazo, y en personas con enfermedades crónicas tales como diabetes mellitus, el síndrome nefrótico, mieloma múltiple, cirrosis hepática o alcoholismo. La efectividad de la vacuna se ha determinado en adultos saludables, y se ha constatado ser 75 al 95 por ciento efectiva. Cuando se estudia la efectividad de la vacuna en grupos no saludables, los análisis estadísticos sugieren una eficacia de 36 por ciento para personas de todas las edades. La efectividad fue más baja en niños entre las edades de 2 a 10 años y en personas con enfermedades pre-existentes que predisponen a infección por el neumococo. La posibilidad de que la efectividad es baja en poblaciones inmunocomprometidas de alto riesgo hace imprescindible evaluar en estos grupos no solo la respuesta de anticuerpos sino la respuesta clínica también.

(Sometido por Carlos H. Ramírez Ronda, MD)

VALUE OF MAXIMAL EXERCISE TEST IN RISK ASSESSMENT OF PRIMARY CORONARY HEART DISEASE EVENTS IN HEALTHY MEN

Bruce RA, De Rowen, TA, Hossack KF. *American Journal of Cardiology* 46: 371-378, 1980.

En este estudio los autores repasan su experiencia en ergometría máxima en 2,365 hombres sin evidencia clínica de cardiopatía. El período promedio de seguimiento fue 5 años y correlacionaron eventos coronarios (infarto, angina, muerte súbita) con la data clínica y ergométrica. Los factores de riesgo coronarios usuales no correlacionaron con eventos coronarios cuando se consideraron individualmente pero la agrupación de varios factores sí correlacionaron con eventos coronarios a cinco años.

Cuatro variables en ergometría máxima correlacionaron con eventos coronarios; dolor de pecho al ejercicio máximo, duración de ejercicio de menos de seis (6) minutos en protocolo de Bruce, frecuencia máxima obtenida de menos de 90 por ciento del máximo predicho para la edad y cambios isquémicos de depresión del segmento ST.

La probabilidad de eventos coronarios en hombres asintomáticos en ausencia de factores de riesgo y con solo uno de los factores ergométricos fue de 1 por ciento en 5 años. Concluyen los autores que en hombres asintomáticos sin factores de riesgo y con electrocardiograma normal al descanso la ergometría es no es buen predictor de eventos coronarios. En pacientes con factores de riesgo o con cuadros clínicos compatible con enfermedad isquémica: la ergometría sí establece probabilidad de eventos subsiguientes.

(Sometido por G. Cintrón, MD, VAH)

Instrucciones para los Autores

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y la del impresor, se requiere de los autores que sigan las siguientes instrucciones:

Manuscrito: El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos a maquina a doble espacio y por un solo lado de cada página, en **TRIPLICADO** y con amplio margen. En página separada deberá incluirse lo siguiente: título, nombre del autor(es) y su grado (ej: MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, y si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse como un encabezamiento al centro y en letras mayúsculas.

Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias.

Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: Introducción, Materiales y Métodos si es aplicable, Observaciones del Caso, Discusión, Resumen (en español e inglés), Reconocimientos y Referencias.

Nomenclatura: Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

Tablas: Las tablas deben aparecer en hojas separadas. Estas deben incluir el título y el número de la tabla (romano). Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales y horizontales en la tabla.

Figuras: Las fotografías y microfotografías se someterán como copias en papel de lustre, sin montar. En el reverso de la figura debe aparecer el número de la figura (arábigo) y el autor y debe indicarse la parte superior.

Referencias: Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los números deben aparecer en paréntesis al nivel de la línea u oración. Al final de cada artículo las referencias deben aparecer en el orden numérico en que se citan en el texto. Estas deben seguir el estilo o patrón del "Index Medicus", el cual se describe a continuación:

Para artículos de Revista:

Apellido(s), e iniciales del autor(es), nombre de la revista, volumen, primera página y año.

Koppisch E.: Bol Asoc Med P Rico 46: 505, 1954.

Para citación de Libros

Apellido(s), e iniciales del autor(es), título, edición, casa editora, ciudad, año y página.

Wintrobe MM: Clinical Hematology, 3rd Ed Lea and Febiger, Philadelphia 1952 p. 67.

Más de tres autores añadir: et al.

Deben usarse solamente las abreviaturas indicadas en el "Cumulative Index Medicus" que publica la Asociación Médica Americana.

Como guía de referencia para preparar su artículo puede usar la publicación Advice to Authors que publica la Scientific Publications Division, American Medical Association, 535 N Dearborn Street, Chicago, Illinois, 60610.

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The Boletín will accept for publication contributions relating to the various areas of medicine, surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the

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Summary of Prescribing Information

***Indications:** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows
"Probably" effective as an adjunct to rest and physical therapy for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Chlorzoxazone does not directly relax tense skeletal muscles in man

Contraindications: Sensitivity to either component

Warnings: Usage in Pregnancy—Use in women of childbearing potential only when potential benefits outweigh possible risks

Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped

Adverse Reactions: Occasionally, drowsiness, dizziness, light-headedness, malaise, overstimulation or gastrointestinal disturbances may be noted, rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, chlorzoxazone may possibly have been associated with gastrointestinal bleeding. While PARAFLEX[®] (chlorzoxazone) tablets and other chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately twenty-seven patients, it was not possible to state that the dysfunction was or was not drug induced.

Usual Adult Dosage: Two tablets q.i.d.

Supplied: Light green tablets, imprinted "McNEIL" and "PARAFON FORTE"—bottles of 100 and 500.

0972

Caution: Federal law prohibits dispensing without prescription. Full directions for use should be read before administering or prescribing.

For information on symptoms/treatment of overdosage, see full prescribing information.

PARAFON FORTE tablets are manufactured by McNeil Laboratories Co., Dorado, PR 00646

References: 1. Wallenstein SL, Houde RW. *Fed Proc* 13 414, 1954. 2. Batterman RC, Grossman AJ. *Fed Proc* 14 316, 1955. 3. Vickers FN. *Gastrointest Endosc* 14 94, 1967. 4. Fein FT. *Ann Allergy* 29 598, 1971. 5. Melke CH, et al. *JAMA* 235 613, 1976. 6. Vernon WG. *Curr Ther Res* 14 801, 1972. 7. Miller AR. *Curr Ther Res* 19 444, 1976. 8. Walker JM. *Curr Ther Res* 15 249, 1973.

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understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

Manuscripts: The entire manuscript, including legends and references should be typewritten double spaced in *TRIPLICATE* with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgment of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

The manuscript should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by center headings in capital letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Material and Methods, Results if indicated, Discussion, Summary in English and Spanish, Acknowledgments if any, and References.

Nomenclature: Generic names of drugs should be used; trade names may also be given in parenthesis, if desired. Metric units of measurements should be used preferentially.

Tables: These should be typed on separate sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical and horizontal lines

should be omitted.

Figures: Photographs and photomicrographs should be submitted as glossy prints, unmounted. They should be labeled in the back with the name of the authors and figure number (Arabic) and the top should be indicated. Legends to the figures should be typed on a separate sheet.

References: These should be numbered serially as they appear in the text. The number should be enclosed in parenthesis on the line of writing and not as superscript numbers. At the end of the article references should be listed in the numerical order in which they are first cited in the text. This list should conform to the Style of the Index Medicus and should be punctuated as in the following examples.

For journal articles:

Surname and initials of author(s), name of journal, volume, first page and year.

Koppisch E: *Bol Asoc Med P Rico* 46: 505, 1954.

For Books:

Surname and initials of author(s), title, edition, publishing house, City, year and page.

Wintrobe MM: *Clinical Hematology*, 3rd Ed Lea and Febiger, Philadelphia 1952 p 67.

More than three authors add: et al.

Abbreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.

For aid in preparing your manuscript refer to the publication *Advice to Authors* available from the Scientific Publications Division, American Medical Association, 535 N Dearborn St., Chicago, Illinois 60610.

TRAUMATIC QUADRIPLÉGIA: FOLLOW-UP STUDY OF SELF-CARE SKILLS

Rogers, JC, Figone, JJ - *Arch. Phys. Med. Rehabil.* 61: 316-321, 80.

El propósito de este estudio fue evaluar en cuanta medida, los pacientes de lesiones al cordón cervical traumática, utilizaban las técnicas de auto cuidado y de los aparatos ortóticos aprendidos en el proceso de rehabilitación, una vez estos pacientes resumieron su vida en la comunidad. Con este propósito se escogieron 35 pacientes y se probaron en el ambiente de su casa entre 1-4 años después de haberse dado de alta, de estos 20 tenían un nivel funcional C6 C7 y 15, C4 C5. Los resultados indicaron que el nivel de auto-cuido logrado durante el proceso de rehabilitación fue mantenido por la mayoría de los pacientes. La mayoría de los pacientes continuaron usando al menos una de las ortosis de extremidad superior. Ni cirugía de mano ni el uso del equipo estaba claramente relacionado al status funcional. Los cambios en ejecución se discuten en términos de re-estructuración de prioridades personales, disponibilidad de apoyo interpersonal y barreras arquitectónicas y de actitudes dentro de la comunidad.

(Sometido por Jesús A. Maldonado, MD)

ANKYLOSING SPONDYLITIS IN WOMEN

Goodman, CE, Lange, RK, Waxman, J., Weiss, TE - *Arch. Phys. Med. Rehabil.* 61: 167-170, 1980.

A pesar de que la espondilitis anquilosante ha sido considerada como condición rara en la mujer, se ha pensado que su incidencia femenina se haya subestimado. En 12 casos estudiados de mujeres portadoras de esta enfermedad se pudo apreciar que los hallazgos clínicos más sobresalientes fueron los siguientes: (1) Comienzo antes de 30 años; (2) Dolor nocturno; (3) Entumecimiento matutino; (4) Dolor articular migratorio e intermitente; (5) Historial de uveítis. La

movilidad de la columna vertebral está limitada en todos estos pacientes. Dolor a la palpación en región sacroilíaca y torácica fueron hallazgos comunes. Cuando todos estos signos claves se presentan, está indicado realizar otras pruebas de laboratorio. La determinación de la presencia del antígeno HLA-B₂₇, el cual se halla en el 90 por ciento de las personas afectadas por la espondilitis anquilosante. Esta prueba es de gran utilidad ya que nos detecta la enfermedad en fase temprana y leve. En 10 de 11 pacientes examinados se encontró una reacción positiva para el antígeno HLA-B₂₇.

Los estudios con radioisótopos pueden demostrar cambios inflamatorios tempranos en la articulación sacroilíaca mucho antes de que pudieran evidenciarlas las radiografías corrientes. En 3 casos estudiados con radiografías simples de la articulación sacroilíaca estas fueron reportadas normales pero al realizarse pruebas con radioisótopos se demostró captación anormal a nivel de la articulación antes mencionada. La detección temprana de la espondilitis anquilosante facilita la instauración de un tratamiento precoz.

(Sometido por R. Aguayo, MD, VAH)

EXTENDED-HEEL SHOES

Evans, David P. - *Rheumatology and Rehabilitation*, 1980, 19, 103-108

Dolor de espalda postural es extremadamente común especialmente en mujeres jóvenes y produce un dolor majadero de poca intensidad pero a menudo persistente por muchos años. Está asociado a músculos abdominales débiles que causan rotación hacia adelante, que a su vez aumenta la lordosis lumbar. Los síntomas mejoran con ejercicios isométricos abdominales. Se ha inventado un zapato (y sandalia) de tacón extendido hacia atrás que permite al paciente ejercitar isométricamente sus músculos cuádriceps femoris y abdominales. En adición permite relajación intermitente de los músculos extensores de la espalda durante paradas prolongadas. Un estudio piloto ha demostrado reducción significativa en la profundidad de la lordosis

lumbar con el uso de este zapato, comparado a un zapato control, durante seis semanas de tratamiento. Todos los casos, aunque de tipo selectivo, se beneficiaron subjetivamente. Los posibles mecanismos de acción son discutidos.

(Sometido por Rafael Alvarez, MD, VAH)

THERMOPLASTIC BODY JACKETS FOR CONTROL OF SPINE AFTER FUSION IN PATIENTS WITH SCOLIOSIS

Sidney L. Wallace and Karl Fillaner, Orthotics and Prosthetics, Sept., 1979, 33: 3: 20-24.

El artículo discute y presenta un "jacket" plástico, liviano que se puede usar en vez de la férula de yeso Risser en pacientes con escoliosis después de fusión espinal. El diseño es moldeado de material termoplástico de 2-3 mm de espesor, extendiéndose anteriormente desde la sínfisis púbica hasta la horquilla esternal y consiste de dos cubiertas laterales que se sobreponen anterior y posteriormente, que permiten ajuste para el crecimiento durante el período promedio de su uso de 9 meses. El artículo describe métodos post-fusión de medir, de fabricación y de ajustar la férula. El uso de este "jacket" plástico por sobre 30 pacientes ha demostrado que radiológicamente es comparable a la férula Risser y que "Subortholen" es preferible a polipropileno en fuerza, maleabilidad y durabilidad. Problemas con su diseño son descritos y 7 fotografías del jacket plástico son incluidas.

(Sometido por Rafael Alvarez, MD, VAH)

TASK PERFORMANCE IN SPINAL CORD INJURY: EFFECT OF HELPLESSNESS TRAINING

Wool, RN, Siegel, D, Fine, PR - Arch. Phys. Med. Rehabil. GI: 321-325, 1980.

Los efectos de fracaso en la ejecución de tareas de pacientes recientemente lesionados en la médula espinal fueron evaluados utilizando la teoría de la ineficacia aprendida como modelo. La teoría postula que los pacientes con un fracaso incontrolable se deprimen y se sienten desválidos mientras que los que tienen un éxito bien controlado desarrollan un sentido de competencia y se sienten útiles. Para proveer validez a esta teoría se tomaron 29 pacientes con trauma reciente a la médula espinal, se entrevistaron y fueron evaluados. Los resultados sugieren que es posible inmunizar a los pacientes de trauma a la médula espinal en contra de las reacciones emocionales debilitantes hasta la parálisis con un régimen de rehabilitación orientado al éxito durante las primeras etapas de recuperación.

(Sometido por Jesús A. Maldonado, MD, VAH)

RELATION BETWEEN LOW BACK PAIN AND RADIOLOGICAL FINDINGS

A. Magora, A. Schwartz, Scand. Rehab. Med., Vol. 12, 1980, No. 2, pp. 47-52.

En un estudio comparativo de 1,024 sujetos con dolor de espalda baja y normales, se encontró pre-expondilolisis (pre-lisis) en 16.4 por ciento, espondilolisis (lisis) en 10.5 por ciento y espondilolistesis (olistesis) en 2 por ciento. No apareció relación entre pre-lisis, lisis y dolor de espalda. Se encontró una aparente relación entre la lisis con la severidad del dolor de espalda. Todos los sujetos con olistesis experimentaron dolor de espalda. Basados en estos resultados, se concluye que lisis y pre-lisis no debe ser base para excluir ningún sujeto de ocupación alguna pero sí la olistesis, y que ambas deben aceptarse como hallazgos radiológicos en los cuales la severidad del dolor puede ser mayor, justificando una ausencia por enfermedad más prolongada.

(Sometido por Miguel Berríos, MD, VAH)

RELATION BETWEEN THE LOW BACK PAIN SYNDROME AND X-RAY FINDINGS

Magora, A., Schwartz, S - *Scand. J. Rehab. Med.* 12: 9-15, 1980.

La relación entre dolor de espalda y espina bífida oculta fue estudiada en 1244 sujetos, de los cuales 800 sufrían dolor de espalda y 440 sirvieron de control. Se comparó edad, sexo, características ocupacionales, curvaturas de la columna vertebral, e historial de trabajo. No hubo evidencia que indicara relación entre dolor de espalda y espina bífida oculta. Se puede descartar la idea de que espina bífida oculta debilita o quita estabilidad a la columna, produciendo dolor e incapacidad. Concluyen los autores que espina bífida oculta es una anomalía congénita de poca importancia en relación con dolor de espalda.

(Sometido por Frank W. López, MD, VAH)

EARLY CHOLECYSTECTOMY FOR ACUTE CHOLECYSTITIS

Jarvinan, H. J., Hastbacka, J - *Ann Surg* 191: 501-505, 1980

Para el tratamiento de colecistitis se recomienda tanto cirugía en los primeros días como después de un "enfriamiento" de la inflamación. En este estudio todos los pacientes que se admitieron con el diagnóstico de colecistitis aguda y que llenaron los criterios de elegibilidad del estudio se randomizaron a cirugía temprana (83 pacientes) o tardía (82 pacientes). Los de cirugía temprana se operaron dentro de los primeros siete días del comienzo de síntomas (un promedio de 1.6 días después de la admisión); los de cirugía tardía se dieron de alta cuando los síntomas se aliviaban y se re-admitieron de 2 a 4 meses más tarde (en promedio, 2.6 meses). No hubo diferencia significativa entre los gru-

pos para: 1. complicaciones operatorias; 2. duración de operación; 3. incidencia de piedras en el ducto común o perforación de la vesícula; 4. morbilidad después de la cirugía; 5. mortalidad. Sin embargo, el grupo de cirugía temprana estuvo hospitalizado un promedio de 7.5 días menos ($p < 0.001$) y el período de incapacidad para trabajar fue un promedio de 14.4 días menos ($p < 0.001$).

(Sometido por Angel Olazábal, MD)

POSTSPLENECTOMY SEPSIS WITH DF-2: REPORT OF A CASE WITH ISOLATION OF THE ORGANISM FROM THE PATIENT'S DOG

Annals of Internal Medicine - 93: 457-459, Sept. 1980.

The authors describe a case of a 44-year-old man with Hodgkin's disease and splenectomy who received chemotherapy and radiotherapy and later developed chills, fever, and rash associated almost immediately with signs and symptoms of septic shock and consumption coagulopathy. Organisms were identified in the buffy coat as beaded gram-negative rods. The patient was treated with penicillin and blood cultures ten days after admission grew a gram-negative bacillus classified as DF-2. When questioned the patient denied being bitten, but admitted that the dog would frequently grasp his hand and arm in its mouth. The organism was recovered from the animal's gingivae. Sepsis with DF-2 organisms is most frequently seen in patients with an underlying condition that impairs host defenses. Physicians should be aware that dog ownership or other animal contact may be a risk factor for DF-2 infection, especially for splenectomized or immunosuppressed patients. Penicillin is the treatment of choice.

(Sometido por R. H. Bermúdez, MD)

MED1 - QUIZ

1. The serum contains ____ of total body potassium.
 - a) 0.4 percent c) 4.0 percent
 - b) 1.4 percent d) 40 percent
2. Which of the following statements is true:
 - a) A potassium supplement is the preferred therapy in asymptomatic patients with secondary hyperaldosteronism.
 - b) Renin inhibits aldosterone secretion by the adrenal cortex.
 - c) Hyperchloremia and metabolic alkalosis usually accompany potassium depletion.
 - d) Aldosterone and sodium are essential to potassium excretion in the distal tubules.
3. In the early stages of diabetic ketoacidosis, serum potassium concentration may be normal or even slightly elevated primarily because:
 - a) Fat cells are an insignificant reservoir of intracellular potassium, and therefore lipolysis does not result in intracellular potassium depletion.
 - b) Concomitant dehydration tends to increase serum potassium concentration.
 - c) Metabolic acidosis causes a rapid potassium shift from the intracellular fluid to the extracellular fluid.
 - d) Glycogenolysis and protein catabolism increase serum potassium concentration.
4. Potassium *chloride* is not preferred for which of the following:
 - a) renal tubular acidosis
 - b) saluretic potassium depletion
 - c) hypochloremic alkalosis
 - d) hypokalemic periodic paralysis
5. Which of the following is contraindicated in patients with esophageal compression:
 - a) K-Lyte/Cl c) Klorvess
 - b) K-Lor d) Slow-K/Kaon-Cl
6. True or False
 - a) ____ A small deficit in total body potassium can significantly reduce serum potassium concentration.
 - b) ____ Metabolic acidosis depletes intracellular potassium.
 - c) ____ Symptoms of hypokalemia rarely occur before the serum potassium has fallen below 3.0 mEq/L.
 - d) ____ Excessive kaliuresis may cause metabolic alkalosis.
 - e) ____ A 24-hour urinary potassium sample is a useful diagnostic tool.
7. The normal values for the following lab reports are PaCO₂ (35-45 mmHg), serum Na (135-155 mEq/L), serum Cl (98-109 mEq/L), serum pH 7.35-7.45). Which of the lab reports is indicative of renal tubular acidosis?

- a) PaCO_2 47; serum Na 145; serum Cl 107; serum pH 7.32
- b) PaCO_2 34; serum Na 138; serum Cl 115; serum pH 7.30.
- c) PaCO_2 46; serum Na 132; serum Cl 90; serum pH 7.48.
- d) PaCO_2 32; serum Na 139; serum Cl 99; serum pH 7.49.
8. Which of the lab reports is indicative of diuretic-induced hypokalemia?
- a) PaCO_2 47; serum Na 145; serum Cl 107; serum pH 7.32.
- b) PaCO_2 34; serum Na 138; serum Cl 115; serum pH 7.30.
- c) PaCO_2 46; serum Na 132; serum Cl 90; serum pH 7.48.
- d) PaCO_2 32; serum Na 139; serum Cl 99; serum pH 7.49.
9. Cushing's Syndrome causes hypokalemia and metabolic _____, whereas pyelonephritis causes hypokalemia and metabolic _____.
10. Match the following:
- _____ spironolactone
- _____ diabetic ketoacidosis
- _____ thiazides
- _____ renal tubular acidosis
- _____ Conn's syndrome
- a. hypochloremic alkalosis
- b. hyperchloremic acidosis
- c. hyperaldosteronism
- d. aldosterone antagonist
- e. normokalemia

(Contestaciones en página 546)

BRIEF COMMUNICATION:

SCORING BEFORE THE BIG GAME DOES NOT TAKE AWAY FROM AN ATHLETE'S PERFORMANCE

When the Minnesota Vikings played the Pittsburgh Steelers in Super Bowl X, the Minnesota Vikings were sequestered from their wives for several days.

The Steelers were allowed to spend the night before the game with their wives in their hotel rooms.

The Vikings proved no match for the Steelers, losing 16-6.

While the outcome of the game was decided by the superiority of the Steelers, the object lesson learned, according to Dr. Donald L. Cooper, was that having sex before the Big Game had absolutely no effect on the eventual outcome.

The idea of not engaging in sexual activity because it will take away from an athlete's performance "is one of the many sports myths that has crept into our society and has been around so long, it is widely accepted as truth," Dr. Cooper said.

But, nothing could be further from the truth according to Dr. Cooper, Director of the Oklahoma State University Hospital and Clinic in Stillwater, and team physician for the Big Eight conference representatives.

"Most team physicians that I have visited with feel that a normal pattern of sexual practice is not detrimental as long as a proper amount of sleep is obtained." Dr. Cooper said.

"The myth," Dr. Cooper said, "was and is strictly adhered to by managers of prize fighters who tried to keep their boxers away from their wives and girl friends for months and weeks at a time."

And abstaining from sexual activity before the big game or big event, Dr. Cooper said, "is part of the mystique known as the All-American Boy Syndrome."

The American Medical Association Committee on Medical Aspects of Sports, which Dr. Cooper headed in 1976, issued a statement several years ago that attempted to relate what is actual fact and what is fiction as far as sex and athletic performance is concerned. In a speech reprinted from the Journal of the American College of Health Association, Dr. Cooper said the AMA Committee "felt that sexual intercourse the night before a game would make no difference in the performance of a married man or any man if intercourse is a regular part of his life style."

In fact Dr. Cooper wrote, "if it would help relax some tension and make it possible for him to sleep better, it could possibly be considered a slight benefit."

In his article entitled, "Can Scoring Influence Athletic Performance?", Dr. Cooper referred to an English team physician Dr. J. G. Williams, who published a book on sports medicine in the 1960s.

In the book, Dr. Williams stated there was no evidence that married couples should alter the normal pattern of their sexual relationships during training periods or during a competitive season. He felt, however, as others have, that under the clandestine circumstances of a one night stand or the emotional pressures of straining to show extra performance in a strange situation, sexual activity

might have a deleterious effect on an athlete's ability to play well.

For those athletes participating in baseball and basketball, said Dr. Cooper, consideration has to be given to the six to eight months of training camp and full weekly schedules.

"I can assure you they are not going to remain celibate during this length of time," Dr. Cooper adds.

Some coaches of other sports that are not participated in to such extent, such as football, soccer, track and wrestling, will keep their players isolated with curfew and bed checks the night before a game or match, Dr. Cooper said.

And almost all college football teams will get the players together either one or two nights before the Big Game to isolate them from others. The same is true of most professional teams

This seclusion with their teammates reinforces the comradeship that binds athletes together, Dr. Cooper explained, and gives an air of "having something special which includes no contact with the opposite sex."

One reason coaches isolate players, Dr. Cooper suggests, "is to try and get the 'mental attitude' right, to have participants get their 'game face' and develop a greater feeling of unity and purpose."

One athlete, Dr. Cooper recalls, Joe Namath, former New York Jet and Los Angeles Rams quarterback said that, both at Alabama and with the pros, he was always isolated the night before a game, but he did admit on a television show that he personally felt his activities at other times did not affect his performance on the football field. He said that he always enjoyed the company of young ladies as friends as well as for possible sexual satisfaction.

But single athletes generally, Dr. Cooper says, do have some real problems in coping

with and handling the frequent and numerous sexual situations they are confronted with.

The late Casey Stengel, who managed the New York Yankees, made the observation once, Dr. Cooper recalled, that "it was not the catchin' that caused the problems for athletes, it was the chasin'." In this vein, Dr. Cooper added, "it would have to get down to what an athlete had on his mind."

Former Olympic discus thrower Olga Gikotva Connelly has said, according to Dr. Cooper, that as far as female athletes were concerned, she felt that if sexual activity was a normal part of her life, it would not affect her performance even if it was the night before. But, if sexual activity was not a part of her normal experience and she was emotionally upset or this was her first sexual experience, it might well affect her performance and concentration.

An ex-major leaguer who admitted that sexual activity caused him to become tired, said he played better when he was tired. In fact, the player was heard to tell another player, according to Dr. Cooper, that his "sinker worked well only when he was tired so he made sure he always was just 'a little tired'." If he was fresh and at full strength, his ball would not sink.

But athletes are not the only ones who have sexual hangups. Dr. Cooper said he once heard a story of a famous opera singer who refused to appear on stage unless she had engaged in sexual activity prior to the performance. Needless to say, she wore out lots of folks around the opera house, Dr. Cooper added.

But many coaches still express alarm about their married players in professional basketball, hockey and baseball following a long road trip which can last from two to three weeks. The coaches reason that their players coming off a long road trip will try to overdo it the first night at home so the next day they

are bound to be a little more tired than usual.

"To my knowledge," Dr. Cooper states, "I do not know of any research data on the hitting ability, shooting ability, or playing ability of athletes who have been on long road trips and then return home." He adds: "With our computers and the well kept data, that might make an interesting project for some

eager graduate student some day. My own personal opinion is that you probably will not find any correlation; but it sure would be an interesting bit of data if I was wrong."

Reprinted from
AMA News Release



I'm your new doctor.

Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Physician's Career Called Demanding

Plan For MD Career

So you want to be a doctor? Many young men and women give some thought to a medical career some time during their growing up years.

What does it take? An American Medical Association pamphlet points out that to become a doctor of medicine demands more of a person in many ways than do many other career choices. To be responsible for the health and sometimes the lives of others at all hours of the day and night, regardless of fatigue or other commitments, takes an enormous amount of dedication and motivation as well as physical and emotional strength.

The high school student who plans to study medicine should be sure to take courses required for admission by most colleges. These almost always include English (preferably four years), several years of laboratory sciences (biology, chemistry, physics), three or four years of math (preferably four) and social studies. Participation in a variety of extracurricular activities also is important, and participation

in a Future Physicians Club, Science Club of America or Medical Explorer Post will help.

In college, the premedical curriculum is more flexible than generally realized. Many students major in biology or chemistry in preparation for medical school, but this is not required.

The college course should include chemistry, biology, physics, math and English. Most accredited colleges and universities offer the course of study needed prior to medical school. About 750 colleges educate most of the medical students in this country. The American Council of Education can provide a list.

The typical medical school curriculum is four years, with the first two years in basic science and the last two in clinical training (working with patients). In recent years the trend in medical education has been toward integrating lecture and laboratory learning with observation, diagnosis and treatment of the patient.

Beyond medical school comes the residency — training in one of the specialties, including family practice. The residency period varies, but the resident usually is eligible for a license to practice medicine after completing the first year.

Many high school and college libraries and most public libraries will be able to provide reference materials for the doctor's career.



October, 1980
Frank Chappell
Science News Editor
AMA

TIGHT CONTROL OF INFLAMMATION



in rheumatoid arthritis* and osteoarthritis:

Tolectin[®] DS

(TOLMETIN SODIUM) DOUBLE STRENGTH
CAPSULES 400MG.



one capsule *t.i.d.*
for a more convenient
starting dose

Double strength, nonsteroidal capsules offer...

- Rapid control of inflammation
- Rapid relief of stiffness and pain
- Dependable, long-term management of chronic symptoms

Peak plasma levels are reached within 30 to 60 minutes. A therapeutic response can be expected in a few days to a week. And *Tolectin* tolmetin sodium is well tolerated: the frequency of milder gastrointestinal adverse effects and tinnitus has been shown to be less than with aspirin.

*For patients classified as Functional Class IV (incapacitated with little or no self-care), safety and effectiveness have not yet been established.

Please turn page for brief summary of prescribing information.

SUMMARY OF PRESCRIBING INFORMATION

TOLECTIN® DS (tolmetin sodium) double-strength capsules— for oral administration

Description: *TOLECTIN DS* (tolmetin sodium) capsules contain tolmetin sodium as the dihydrate in an amount equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium.

Contraindications: *Tolmetin* (tolmetin sodium) should not be used in patients who have previously exhibited intolerance to it or patients in whom aspirin and other non-steroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria.

Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported.

If *Tolmetin* must be given to patients with active peptic ulcer, closely supervise the patients for signs of ulcer perforation or severe gastrointestinal bleeding.

Precautions: *General*—Clinical studies of up to two years duration have shown no changes in the eyes attributable to *Tolmetin* (tolmetin sodium) administration, however, because of ocular changes observed clinically with other non-steroidal anti-inflammatory drugs, ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.

There has been no evidence of renal toxicity to date in clinical studies, however, since *Tolmetin* is eliminated primarily by the kidneys, closely monitor patients with impaired renal function, they may require lower doses.

Tolmetin prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when *Tolmetin* is administered.

In patients receiving concomitant *Tolmetin*-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

Tolmetin should be used with caution in patients with compromised cardiac function.

The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g. sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips (e.g. Albustix®, Uristix®, etc.).

Usage in Pregnancy—Since *Tolmetin* has not been studied in pregnant women, the use of *Tolmetin* during pregnancy is not recommended.

Nursing Mothers—Because *Tolmetin* may be secreted in human milk, as a general rule nursing should not be undertaken while a patient is on this drug.

Drug Interactions—Although *Tolmetin* has been found *in vitro* to bind extensively to plasma protein, it does not alter the dosage of warfarin required to maintain a uniform prothrombin time.

In adult diabetic patients under treatment with either sulfonylureas or insulin, there is no change in the clinical effects of either *Tolmetin* or the hypoglycemic agents.

Adverse Reactions: Gastrointestinal System—The most frequent adverse reactions which occurred were gastrointestinal: nausea, 1 in 9 patients; dyspepsia, 1 in 10 patients; abdominal pain, 1 in 15; gastrointestinal distress, 1 in 15; flatulence, 1 in 25; diarrhea, 1 in 25; constipation, 1 in 40; vomiting, 1 in 30; gastritis, 1 in 55; and significant gastrointestinal bleeding without evidence of peptic ulceration, 1 in 240.

The incidence of peptic ulcer in about 3000 patients treated up to two years in clinical studies was about 1 in 50. Thirty-four percent of the ulcer patients had prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs, including corticosteroids, known to produce peptic ulceration.

In clinical trials about 10% of patients dropped out because of adverse reactions, mostly gastrointestinal in nature.

Body as a Whole—headache, about 1 in 10 patients; asthenia and chest pain, less frequently; and, rarely, anaphylactoid reactions.

Cardiovascular—edema, about 1 in 15 patients; hypertension, less frequently.

Central Nervous System/Psychiatric—dizziness or lightheadedness, about 1 in 20 patients; tension or nervousness, 1 in 50 patients; drowsiness, 1 in 60 patients; insomnia and depression, less frequently.

Dermatologic—rash, about 1 in 40 patients; pruritus, 1 in 60 patients; skin irritation, 1 in 55 patients.

Special Senses—tinnitus, about 1 in 65 patients.

Hematologic—Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred. This is similar to that reported with other non-steroidal anti-inflammatory drugs. A few cases of granulocytopenia have been observed.

Caution: Federal law prohibits dispensing without a prescription.

Full directions for use should be read before administering or prescribing.

For information on symptoms and treatment of overdose, see full prescribing information.

Also available: *TOLECTIN®* (tolmetin sodium) tablets 200 mg. *DEPOT STOCKED 500's*

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Office on Smoking and Health
Public Health Service Rockville, MD 28057

CURSO - NOTICIAS

PEDIATRIC UPDATE - 1981 - The 11th Pediatric Postgraduate Seminar - February 28 - March 8, 1981, Marbella, Spain.

For additional information please contact James E. Mulvihill, D.M.D., Long Island Jewish-Hillside Medical Center, New Hyde Park, New York 11042, (212) 470-2111.

AMA NEWS:

CAT SCANNERS SAVE MONEY IN TREATING CANCER

CHICAGO — Computerized tomography — hailed as a major advance in medical technology but also held up as a prime example of why medical costs have risen — actually saves money when used to guide the radiation treatment of cancer, says a report in the Sept. 19 Journal of the American Medical Association.

The machines, known popularly as Cat Scanners, are expensive, costing upwards of half a million dollars. When they first became available in the 1970s, every hospital immediately wanted one. But many critics questioned whether the machines would ever become cost effective.

Dr. Michael Goitein of Massachusetts General Hospital, Boston, reports on a study in which he found that use of the whole-body scan to easily and accurately delineate malignant tumors actually saves money in the long run.

A body scan costs around \$250, Dr. Goitein reports. Cost of therapy which follows the body scan probably averages \$12,000 for cancer treatment. But total cost of treatment when local control of the tumor fails is estimated at \$36,000. There are many fewer failures of initial treatment when the exact diagnosis of the CT scan is available to the doctor.

With use of the CT scan, there is a better than

even chance that the resulting therapy will bring local control of the tumor. This knowledge is gained at a cost of \$250 in a treatment program that will cost \$12,000 altogether. Thus, he says, it would be poor economy indeed to fail to use the scanner to save money on health care costs. When the initial treatment fails, there is an additional \$24,000 in costs required to cope with the tumor.

"It no longer seems reasonable to question whether CT has an important role to play in the treatment of malignant disease," Dr. Goitein declares.

LEUKEMIA INCREASE NOTED IN MILITARY MEN

CHICAGO — An almost three-fold increase in leukemia cases among military men participating in maneuvers in Nevada during the 1957 nuclear test explosion "Smoky" is noted in a report in the Oct. 3 Journal of the American Medical Association.

Nine cases of leukemia have occurred among 3,224 men who participated in the maneuvers, says Glyn G. Caldwell, M. D., of the Center for Disease Control, Atlanta. This represents a "significant increase" over the expected incidence of 3.5 cases, he declares.

Many details are not yet clear.

"If not a chance occurrence, the apparent excess of leukemia among Smoky participants suggests that such persons may have received more radiation than previously supposed or that low doses of radiation may be more carcinogenic than past estimates predicted," Dr. Caldwell points out.

SUNLIGHT HARMFUL TO SKIN, PHYSICIANS ARE REMINDED

CHICAGO — Stay out of the suntanning parlors. In fact, stay out of the sun.

"It is the physician's duty to inform patients of the great dangers of repeated assaults on the skin by harmful ultraviolet light, whether its source is the ancient sun or the new neighborhood suntanning salon," says a report in the Sept. 12 Journal of the American Medical Association.

The light rays cause premature aging and wrinkling of the skin, and they cause skin cancer, says Lewis H. Kaminester, MD, of North Palm Beach, Fla.

What the light rays do to the skin is frightening, according to Dr. Kaminester.

"Solar degeneration of the skin produces wrinkling, atrophy (thinning of the skin), hyperpigmented and hypopigmented macules, telangiectases, yellow papules and plaques, and solar keratoses." These big words mean that the skin is sorely damaged. And the solar keratoses often are the first stage of skin cancer.

"There is clear evidence implicating solar radiation, whether its source be sunlight bulbs or natural sunlight, as a factor in inducing skin cancers," Dr. Kaminester says.

The frequency of three of the most common types of skin cancers is higher on sun-exposed parts of the body — face, neck, hands, he says.

Clearly, the more solar irradiation a person gets, the higher his chances are of having a skin cancer develop sometime in the future. Sometimes the cancer may not show up until the individual is age 60 years, but if he is light-skinned and blonde, it may come much sooner.

"The problem for the person in quest of the golden tan is that he or she may not be aware of future detrimental consequences of repeated exposure to ultraviolet light."

TUBERCULIN TEST DISCOUNTED IN SCREENING FOR DISEASE

CHICAGO — The tuberculin test should be abandoned as a screening procedure for tuberculosis, the editor of the Journal of the American Medical Association declares in an editorial in the Sept. 5 issue.

The tuberculin test is useful when tuberculosis is suspected, but has little value as a screening test today, says William R. Barclay, MD. The prevalence of tuberculosis is so low in 1980 that screening is not cost effective, and administration and interpretation of the test often is so erratic that results of such screening are not dependable, he says.

Tuberculosis has declined substantially, but some cases remain. The tuberculin test is one of a number of procedures that the physician may use to arrive at a diagnosis, but the most important step is to think of the disease as possible cause of a patient's illness, Dr. Barclay advises fellow physicians.

The problem with the tuberculin test is that it is not conclusive. A negative test does not rule out tuberculosis, and a positive test does not confirm the existence of active infection, he says.

The editorial accompanies a report by Charles S. Bryan, MD, of the University of South Carolina School of Medicine, Columbia.

There are not national guidelines for the test, Dr. Bryan says, and it is handled differently in individual hospitals. The test as now administered is likely to be not only misinterpreted but also uninterpreted, he says.

VITAMIN E FOUND HELPFUL IN NONCANCEROUS BREAST LUMPS

CHICAGO — Vitamin E relieves noncancerous breast lumps, says a report in the Medical News section, Sept. 5 Journal of the American Medical Association.

Noncancerous lumpy breast tissue plagues up to 20 per cent of American women, says the report. This disorder is often called fibrocystic breast disease, and sometimes is also known as mammary dysplasia

or fibrous mastopathy.

Women with at least some types of fibrocystic breast disease are thought to be at a twofold to eightfold greater risk of developing breast cancer. Even those whose lumps remain benign often experience extreme discomfort. Breasts ache and become quite tender.

Robert S. London, MD, director of reproductive endocrinology at Baltimore's Sinai Hospital and faculty member of The Johns Hopkins University School of Medicine, told JAMA of experience in prescribing Vitamin E for these patients over a period of several

years. Earlier studies had reported some success.

In the most recent study by the Hopkins group, 26 patients were treated. Ten responded well, 12 recorded fair response and the others did not respond. Good response meant that the lumps went away, along with the discomfort, Dr. London says.

On the basis of current findings, Dr. London recommends that physicians try prescribing Vitamin E for their patients with cystic breast disease. It worked in a high percentage of patients and no side effects were noted, he says.

ANUNCIO

Disponible para arrendamiento un local habilitado para oficinas en el primer piso del edificio ubicado en la Calle Tetuán Núm. 150 en el Viejo San Juan. Facilidades debidamente acondicionadas y decoradas para dos ejecutivos, con espacio para tres secretarias, salón de recepción, salón de archivos, dos baños y acceso directamente a la Calle Tetuán. Totalmente alfombrado, con cortinas y equipo de acondicionar aire y está disponible para arrendamiento inmediatamente.

Para más información llamar a : teléfonos 725-7481; 725-7482 o 725-7483 o a la siguiente dirección: William Estrella Law Offices, P. O. Box S-4826, San Juan, Puerto Rico 00905; Calle Tetuán Núm. 150, segundo piso, San Juan, Puerto Rico 00901.

Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Prostate Trouble Is Common Male Ill

Prostate Hits Men

After age 50, approximately one in three men will have prostate trouble.

The principal manifestation is difficulty in urination.

Medical management will help about half of these men. The others can be helped only by surgery.

The problem is an enlargement of glands surrounding the urethra, the tube through which urine passes. This constricts the tube and interferes with flow of urine.

What causes this enlargement is not known. We do know that enlarged prostates are not caused by sexual excesses, masturbation or gonorrhea, as is popularly believed, the American Medical Association says.

As the gland slowly enlarges, urination becomes more and more difficult. The stream of urine lacks force and becomes weak and dribbly. There may be a feeling

of inability to empty the bladder. This may cause pain or blood in the urine, and an urgent need to urinate frequently.

There is no medicine that will "dissolve" or materially help an enlarged prostate. Infections can be treated, and in the early stages massage of the prostate may be useful. But if sufficient obstruction to the passage of urine creates complications, surgery becomes necessary.

The operation through the urethra is now the most widely used of all prostate operations. A lighted tube is passed through the urethra and through this appropriate instruments can be passed which the surgeon will use to cut or cauterize or perform other procedures needed to remove enlarged parts of the glands.

Prostate trouble can be real trouble, but it need not be if it is discovered early, its development is observed and surgery is performed before future health is damaged or frequency and urgency of urination interfere with a man's normal life. Every man over 50 should ask his doctor to check the prostate as part of every health examination.



March, 1980
Frank Chappell
Science News Editor
AMA

WANTED: Physicians who prefer medicine to paperwork.

We are looking for dedicated physicians, physicians who want to be, not salesmen, accountants, and lawyers, but physicians. For such physicians, we offer a practice that is practically perfect, where in almost no time you experience a spectrum of cases some physicians do not encounter in a lifetime, where you work without worrying whether the patient can pay or you will be paid, and where you prescribe, not the least care, nor the most defensive care, but the best care.

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Controls disturbed behavior in nursing home patients without undue sedation*

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such as irrational behavior, confused thinking, agitation, hyperactivity, emotional withdrawal, hostility, suspiciousness.

"The ability of haloperidol [HALDOL[®]] to control troublesome symptomatology while preserving alertness and sociability would contribute significantly toward satisfying treatment goals and providing a better quality of daily life for the geriatric patient."

Smith GR et al. *Psychosomatics* 15 138, 3rd quarter, 1974

Minimizes likelihood of cardiovascular complications,** uncomfortable anticholinergic effects

"The lack of hypotensive effects ...suggests that haloperidol may be preferable to the phenothiazines in the treatment of mental disorders in the aged."

Tobin JM et al. *Geriatrics* 25(6):122, 1970.

"Among the antipsychotic drugs...haloperidol has the lowest anticholinergic potential."

Bernstein JG. *Clinical Psychopharmacology*
Littleton, MA, PSG Publishing Company, 1978, p 123

Especially useful for treating elderly patients with concomitant diseases

Unlike some of the other major tranquilizers, HALDOL haloperidol may be used concomitantly with other medications frequently prescribed for geriatric patients.

"There really are no drug interactions of major clinical importance involving haloperidol, which is a rather unique advantage of this drug."

Bernstein JG: *Management of Side Effects Related to Antipsychotic Drug Therapy* An Interview, 1978, p 12.

*Although some instances of drowsiness have been reported, marked sedation is rare.

**Transient hypotension occurs rarely; severe orthostatic hypotension has not been reported.

Note: Extrapyramidal symptoms, when they occur, are readily controllable with antiparkinson drugs or dosage adjustment.

Please turn page for summary of prescribing information. Photograph posed by professional model.



HALDOL[®] (haloperidol) *contain FD&C Yellow No. 5 (see Precautions)

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A dosage form for every therapeutic need

Summary of Prescribing Information

Contraindications: Severe, toxic CNS depression or comatose states from any cause, hypersensitivity to the drug, Parkinson's disease.

Warnings: Usage in Pregnancy: Safe use in pregnancy or in women likely to become pregnant has not been established, use only if benefit clearly justifies potential hazards. Infants should not be nursed during drug treatment.

Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity.

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL haloperidol may block its vasopressor activity and paradoxical further lowering of blood pressure may occur); (2) receiving anticonvulsant medication since HALDOL haloperidol may lower the convulsive threshold; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants. Concomitant antiparkinson medication, if required, may have to be continued after HALDOL haloperidol is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL haloperidol. When HALDOL haloperidol is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL haloperidol. FD&C Yellow No. 5 (tartrazine) may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Adverse Reactions: CNS Effects: Extrapyramidal Reactions. Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug

may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn.

Persistent Tardive Dyskinesia: Although rarely reported with HALDOL haloperidol, tardive dyskinesia may appear during or after long-term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and sometimes appear irreversible; there is no known effective treatment and all antipsychotic agents should be discontinued. The syndrome may be masked by reinstitution of drug, increasing dosage, or switching to a different antipsychotic agent.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms.

Cardiovascular Effects: Tachycardia and hypotension. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice reported. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia and hypoglycemia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention and diaphoresis. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration.

The injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

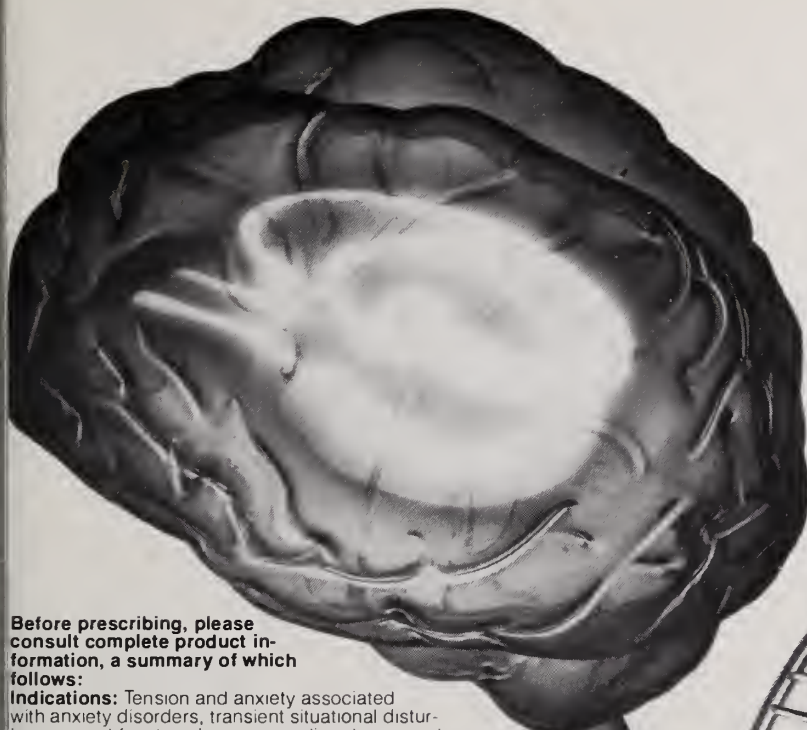
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IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

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Only Valium® (diazepam/Roche)
is indicated in anxiety
and tension states
and as an
adjunct in the
relief of skeletal
muscle spasm

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety associated with anxiety disorders, transient situational disturbances and functional or organic disorders; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. **Adults:** Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10, Prescription Paks of 50, available in trays of 10.

General guidelines
for the prescribing
and appropriate use of
minor tranquilizers

- Individualize dosage for maximal beneficial effect.
- Prescribe the specific quantity needed until the next checkup period, schedule frequent, periodic reexaminations to monitor results of therapy.
- Establish treatment goals and gradually discontinue medication when these have been met.
- Avoid prescribing for individuals who appear dependency-prone or whose histories indicate the potential for misuse of psychoactive substances, including alcohol.
- Caution patients against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving.
- Advise patients against the ingestion of alcoholic beverages while undergoing therapy with minor tranquilizers.
- Counsel patients to follow label directions, keep medication out of children's reach, and dispose of unused or old medication.
- Caution patients against giving medication to others.
- Avoid abrupt cessation of extended therapy by tapering dosage before discontinuing medication.



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ASOCIACION MEDICA DE PUERTORICO

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HAIRY CELL LEUKEMIA - CASE REPORT AND REVIEW OF THE LITERATURE

DURATION OF ACTION OF AN ANTACID IN TWO GROUPS OF PATIENTS

LIVER SCANNING IN THE PRE-OPERATIVE EVALUATION
OF THE PATIENTS WITH GYNECOLOGICAL MALIGNANCIES

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ABSTRACTOS DE LITERATURA MEDICA

FORO DE MEDICINA NUCLEAR:
HEPATIC RADIOXENON ACCUMULATION IN AN ALCOHOLIC PATIENT

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INDICE PAGINA 560

VOL. 72

NUM. 11

NOVIEMBRE 1980

half-life

Just one built-in advantage

Ensures smooth therapeutic effect even if a dose is missed The relatively longer half-life of Valium® (diazepam/Roche) has important clinical and pharmacological implications. Steady-state levels generally are reached within 5-7 days with no further accumulation. At this plateau, the patient benefits from the consistent, steady response you expect. Sharp blood level variations, frequently attributed to agents with a short half-life, do not appear with Valium.

Avoids sudden symptom breakthrough

Once steady-state levels are achieved, sudden reemergence of symptoms is unlikely. Diazepam and its active metabolites exhibit overlapping half-lives that are advantageous not only during therapy but especially when pharmacologic support is discontinued.

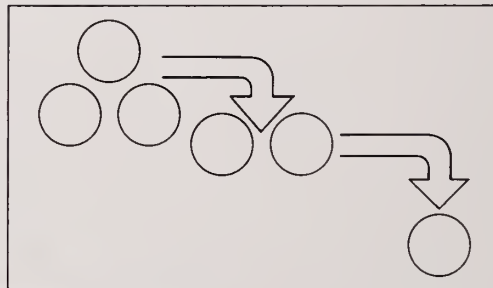
Elimination rates are gradual with Valium and thus provide a compatible adjustment interval for

the patient. In comparison, blood levels of short-acting agents with inactive metabolites decrease more rapidly and are more likely to be associated with withdrawal symptoms if medication is stopped abruptly.* With Valium unwanted effects other than drowsiness or ataxia are rare. Patients should be cautioned about driving and advised to avoid alcohol.

Tapers naturally; complements gradual dosage reduction at discontinuation

When any psychoactive medication is discontinued, it is good medical practice to gradually reduce the dosage. From your own experience you know this is rarely necessary after a short course of Valium therapy, but for patients on extended therapy, gradual reduction of dosage is advisable. This regimen, along with the self-tapering feature of Valium, provides a smooth transition to independent coping.

*Sellers EM: *Drug Metab Rev* 8(1):5-11, 1978



*in the management of
symptoms of anxiety*

Valium®
diazepam/Roche
2-mg, 5-mg, 10-mg scored tablets

*effective therapy through
efficient pharmacodynamics*

Before prescribing, please see summary of product information on next page



Valium[®] diazepam/Roche

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal, adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy)

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Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication. abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.

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for oral administration

Description: *TOLECTIN DS* (tolmetin sodium) capsules contain tolmetin sodium as the dihydrate in an amount equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium.

Contraindications: *Tolmetin* (tolmetin sodium) should not be used in: patients who have previously exhibited intolerance to it or patients in whom aspirin and other non-steroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria.

Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported.

If *Tolmetin* must be given to patients with active peptic ulcer, closely supervise the patients for signs of ulcer perforation or severe gastrointestinal bleeding.

Precautions: *General*—Clinical studies of up to two years duration have shown no changes in the eyes attributable to *Tolmetin* (tolmetin sodium) administration; however, because of ocular changes observed clinically with other non-steroidal anti-inflammatory drugs, ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.

There has been no evidence of renal toxicity to date in clinical studies; however, since *Tolmetin* is eliminated primarily by the kidneys, closely monitor patients with impaired renal function; they may require lower doses.

Tolmetin prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when *Tolmetin* is administered.

In patients receiving concomitant *Tolmetin*-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

Tolmetin should be used with caution in patients with compromised cardiac function.

The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g. sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips (e.g. Albustix®, Uristix®, etc.).

Usage in Pregnancy—Since *Tolmetin* has not been studied in pregnant women, the use of *Tolmetin* during pregnancy is not recommended.

Nursing Mothers—Because *Tolmetin* may be secreted in human milk, as a general rule nursing should not be undertaken while a patient is on this drug.

Drug Interactions—Although *Tolmetin* has been found *in vitro* to bind extensively to plasma protein, it does not alter the dosage of warfarin required to maintain a uniform prothrombin time.

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Adverse Reactions: Gastrointestinal System—The most frequent adverse reactions which occurred were gastrointestinal: nausea, 1 in 9 patients; dyspepsia, 1 in 10 patients; abdominal pain, 1 in 15; gastrointestinal distress, 1 in 15; flatulence, 1 in 25; diarrhea, 1 in 25; constipation, 1 in 40; vomiting, 1 in 30; gastritis, 1 in 55; and significant gastrointestinal bleeding without evidence of peptic ulceration, 1 in 240.

The incidence of peptic ulcer in about 3000 patients treated up to two years in clinical studies was about 1 in 50. Thirty-four percent of the ulcer patients had prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs, including corticosteroids, known to produce peptic ulceration.

In clinical trials about 10% of patients dropped out because of adverse reactions, mostly gastrointestinal in nature.

Body as a Whole—headache, about 1 in 10 patients; asthenia and chest pain, less frequently; and, rarely, anaphylactoid reactions.

Cardiovascular—edema, about 1 in 15 patients; hypertension, less frequently.

Central Nervous System/Psychiatric—dizziness or lightheadedness, about 1 in 20 patients; tension or nervousness, 1 in 50 patients; drowsiness, 1 in 60 patients; insomnia and depression, less frequently.

Dermatologic—rash, about 1 in 40 patients; pruritus, 1 in 60 patients; skin irritation, 1 in 55 patients.

Special Senses—tinnitus, about 1 in 65 patients.

Hematologic—Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred. This is similar to that reported with other non-steroidal anti-inflammatory drugs. A few cases of granulocytopenia have been observed.

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EFFECT OF ETHANOL ON THE GASTRIC MUCOSA IN NORMAL AND CIMETIDINE-TREATED DOGS

Angel Olazábal, MD and Luiz Nascimento, MD

Summary: The effects of ethanol (40 percent) on the gastric potential difference and net fluxes of electrolytes through the gastric mucosa were studied in controls and cimetidine (40mg/kg) treated dogs. Ethanol instillation to the gastric mucosa significantly increased the net fluxes of sodium and potassium. Cimetidine administration alone decreased the net fluxes of sodium and potassium and significantly raised the potential difference. Ethanol instillation to cimetidine group significantly increased the sodium and potassium despite significantly lower basal values for ion fluxes and higher gastric potential difference. The effect of ethanol on the gastric potential difference was similar in both groups; following ethanol instillation the gastric potential difference significantly decreased to identical levels. These results indicate that pre-treatment with cimetidine is unable to prevent the effects of ethanol on the gastric potential difference and net fluxes of electrolytes.

Resumen: Se estudió el efecto de etanol (40 por ciento) en algunas funciones fisiológicas

de la mucosa gástrica de perros y el efecto que tratamiento con cimetidina (40mg/kg, endovenosamente) tenía sobre los efectos de etanol. Etanol aumentó significativamente el flujo neto de iones de sodio y potasio hacia el lumen y redujo el diferencial en potencial a través de la pared gástrica. La administración de cimetidina solamente produjo una disminución significativa en el flujo neto de iones de sodio y potasio y elevó el potencial a través del estómago. Administración de etanol media hora después de la dosis de cimetidina resultó en un aumento significativo del flujo neto de iones de sodio y potasio hacia el lumen y en una disminución significativa en el potencial de la pared gástrica. Estos resultados indican que una dosis de cimetidina dada 30 minutos antes de exponer el estómago a etanol no previene los efectos de etanol en las funciones gástricas estudiadas.

Introduction

The gastric mucosa functions as a barrier to the diffusion of H⁺ and other ions (1-3). Previous studies by Davenport and others (4-8) have described the physiological and anatomical consequences of breaking this barrier. The topical application of gastric mucosal breakers results in epithelial damage. A decrease in the transmembrane potential difference (11), profound alterations in sodium and potassium transport and abnormal hydrogen ion secretion

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have been described with ethanol (4, 5, 7).

The H₂ receptor antagonist cimetidine in the rat protects the gastric mucosa against aspirin-induced damage (9, 10). This effect may be due solely through inhibition of acid secretion (9) although a cytoprotective effect has been proposed (10). We have examined the effect of ethanol on the gastric mucosal barrier of control and cimetidine treated dogs by determining the changes in the net fluxes of ions and in the potential difference across the mucosa.

Materials and Methods

Dogs were fasted for 18 hours and anesthetized with sodium pentobarbital (25mg/kg); anesthesia was maintained with administration of small doses when needed. The animals were intubated and connected to a Harvard respirator. A nasogastric tube with an attached electrode was placed in the stomach. Through a midline incision the pylorus and the cardio-esophageal junction were ligated tightly. The tip of nasogastric tube was placed in the proximal half of the stomach. A reference electrode was placed in a femoral vein. The gastric transmucosal potential difference was measured as previously described (3, 8). We used a Beckman potentiometer connected to a linear chart recorder (Beckman Instruments, Inc., Fullerton, CA.). All animals had the fasting gastric contents aspirated and discarded. The stomach was then washed with deionized water and emptied completely. The gastric potential difference was recorded for 30 minutes to establish a control value and the stomach contents collected. Two groups of animals were studied:

GROUP I - Following the control period six dogs were given 10ml of normal saline intravenously over a two minute period and the gastric potential difference recorded continuously for 90 minutes. Thirty minutes after the saline infusion the gastric contents were collected and measured. Emptying of the stomach contents was obtained by several aiding maneuvers

such as insufflation of air, tilting of the surgical table and/or slight external manipulation of the stomach with concomitant aspiration. Immediately after, ethanol (30ml, 40 percent) was introduced into the stomach through the nasogastric tube. After two periods of 30 minutes each, samples were collected following ethanol instillation. At the end of the first 30 minute period all the gastric contents were aspirated. During the second period ethanol was not added to the gastric lumen.

GROUP II - Following control period ten dogs were studied in an identical fashion except that cimetidine (40mg/kg diluted in 10ml of saline) was given intravenously over two minutes.

Sodium and potassium concentrations in the gastric contents were measured using a Beckman Flame Photometer. The fluxes of sodium and potassium in the recovered fluid were calculated by multiplying the electrolyte concentration determined in the gastric content by the volume collected in 30 minutes. The data are expressed in $\mu\text{Eq}/30\text{min}$. The results were compared using the "t" test for either paired or unpaired data. A p value of < 0.05 was considered significant. Data are presented as SEM.

Results

Table I summarizes the results in Group I. As can be seen net sodium flux from a baseline of $132 \pm 39 \mu\text{Eq}/30\text{min}$ significantly increased following ethanol instillation to values of 540 ± 102 and $654 \pm 180 \mu\text{Eq}/30\text{min}$ at 30 and 60 minutes respectively ($p < 0.05$).

Net potassium flux increased from a control value of $6.3 \pm 2.7 \mu\text{Eq}/30\text{min}$ to 33 ± 12 at 30 minutes and to $29.4 \pm 7.8 \mu\text{Eq}/30\text{min}$ at 60 minutes ($p < 0.05$). Thus, ethanol instillation to the stomach of normal dogs significantly increased luminal net fluxes of sodium and potassium.

Table II summarizes the results obtained in Group II. Following cimetidine administration the basal net sodium flux was 22.5 ± 6

TABLE I

Sodium and Potassium Net Fluxes during Control and Ethanol

	Control	Ethanol	
		30 Min	60 Min
Na+	132±39	540±102*	654±180*
N=6			
K+	6.3±2.7	33±12*	29.4±7.8*

Fluxes expressed as $\mu\text{Eq}/30\text{min.} \pm \text{SEM}$.

*Statistical difference from controls; see text.

TABLE II

Sodium and Potassium Net Fluxes during Cimetidine and Ethanol

	Cimetidine	Ethanol	
		30 Min	60 Min
Na+	22.5±6	225±54*	273±69*
N=10			
K+	3.6±1.2	19.2±5.1*	11.1±2.1*

See Table I.

$\mu\text{Eq}/30\text{min}$ a significant lower value than control. Ethanol instillation elicited a significant increase in sodium flux $225 \pm 54 \mu\text{Eq}/30\text{min}$ (10 fold increase) and this effect persisted through the second 30 minute period, $273 \pm 69 \mu\text{Eq}/30\text{min}$ ($p < 0.02$).

After cimetidine, the net potassium flux was lower than control $3.6 \pm 1.2 \mu\text{Eq}/30\text{min}$.

Following ethanol instillation a significant increase in potassium flux also occurred 19.2 ± 5.1 and $11.1 \pm 2.1 \mu\text{Eq}/30\text{min}$ at 30 and 60 minutes respectively ($p < 0.02$). Thus, cimetidine alone decreased the luminal fluxes of sodium and potassium but did not prevent a significant increase in electrolytes fluxes elicited by ethanol. Thus, ethanol increases

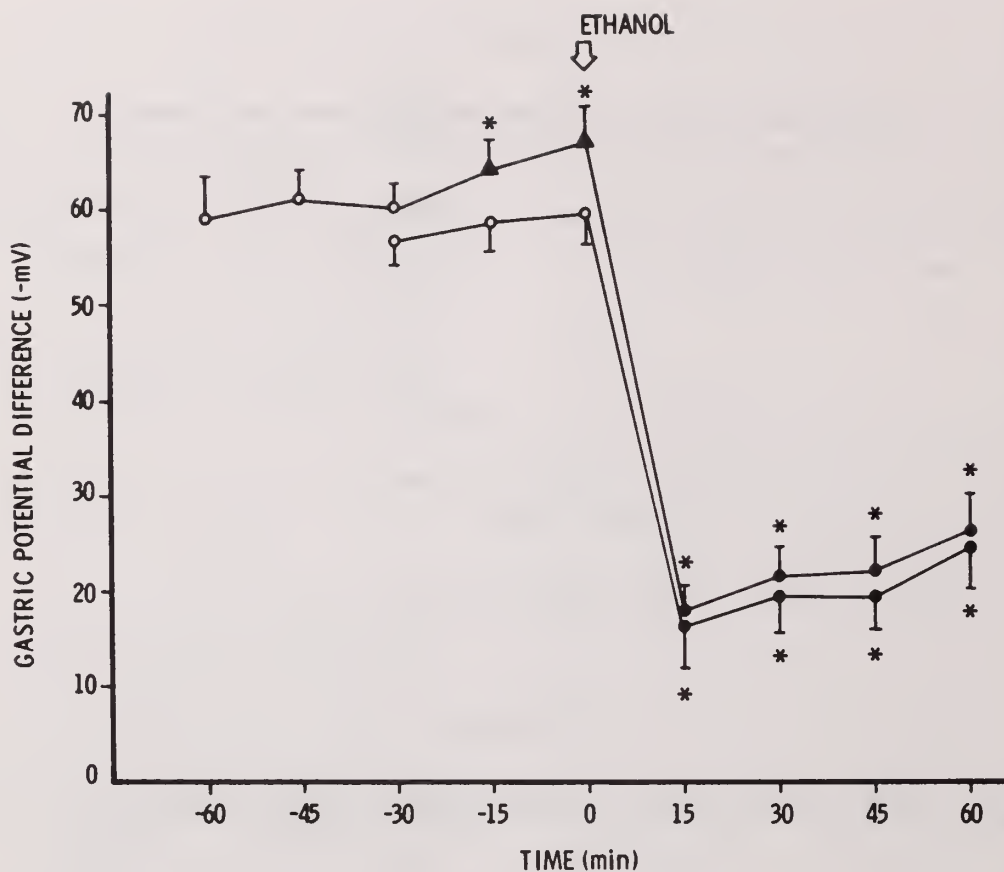


Figure 1: Effect of ethanol (black dots) on gastric potential difference in control (open circles) and cimetidine (black triangles) treated dogs. *denotes statistical significant differences.

the fluxes of Na and K in cimetidine treated dogs although the absolute numbers are set at lower levels in this group.

Figure 1 summarizes the gastric potential difference results obtained in Group I and II. During control conditions the gastric potential difference was identical in both groups. Cimetidine administration elicited a small but significant increase in gastric potential difference. Ethanol alone (Group I) or after cimetidine (Group II) significantly decreased the gastric potential difference. In addition these changes persisted throughout the experiments in both groups

Thus, cimetidine did not prevent the gastric potential difference alterations caused by ethanol instillation. Moreover, the recovery phase was not different in the two groups.

Discussion

Our results clearly confirm that ethanol instillation to the gastric mucosa of dogs significantly increases the luminal effluxes of sodium and potassium under control conditions and in the cimetidine treated dog. Cimetidine alone in the dose administered signi-

ificantly decreased the net effluxes of ions to the gastric lumen. This effect was clearly demonstrable by the lower basal values following cimetidine being significantly lower than controls. These changes in ion fluxes were associated with significantly higher potential difference values. Our results also demonstrated that ethanol instillation to the gastric mucosa significantly decreased the potential difference to similar levels in both groups. Altogether, these findings indicate that pretreatment with cimetidine does not prevent the ethanol effect on gastric potential difference and sodium and potassium fluxes. This significant effect observed in the cimetidine group was, however, set at a lower level than in the control group.

Studies by Davenport (1, 4, 5) and others (7, 11) have demonstrated that ethanol significantly alters the transport of ions across the gastric mucosal barrier. These studies clearly showed that ethanol significantly enhanced H^+ secretion and the fluxes of sodium and potassium to the gastric lumen. In elegant experiments utilizing the Heidenhain pouch these authors demonstrated that the reason for a decrease in the intraluminal H^+ concentration following ethanol was due to an excessive back diffusion of acid (1). In addition it was determined that the threshold concentration at which ethanol alters the ion fluxes through the canine oxyntic glandular mucosa lies above 8 percent and below 14 percent (4). It was evident by our findings that ethanol (40 percent) damaged the gastric mucosa barrier as judged by the alterations in sodium and potassium effluxes.

The transmural gastric mucosal potential difference is an indicator of the integrity of the gastric mucosa. Guth et al (10) suggested that cimetidine has an effect on the gastric mucosal barrier independent of H^+ secretion mechanism. This protective effect was postulated in studies involving aspirin

action in the gastric mucosa of the rat. Conversely, Carmichael et al (9) did not observe such effect under the same experimental conditions and suggested that in the rat cimetidine elicited its effect through an action on H^+ secretion. We failed to demonstrate a preventive effect for cimetidine in the gastric mucosa of the dog following ethanol instillation. Pre-treatment with cimetidine did not attenuate the fall in gastric potential difference or diminish the magnitude of change in the flux of ions. Despite differences in species and the agent used our studies support the findings of Carmichael and co-workers (9).

Of notice is the fact that the cimetidine treated group prior to ethanol administration had a lower efflux of sodium and potassium and a significantly higher gastric potential difference. Despite these differences following ethanol the changes in potential difference were similar in both groups. This data strongly suggests that under these experimental conditions the cimetidine effect on gastric ion fluxes and potential difference are unable to prevent the action of ethanol upon the gastric mucosa.

In summary our data showed that: 1. intravenous cimetidine administration to dogs significantly increased gastric potential difference and decreased the net fluxes of sodium and potassium to the lumen; 2. ethanol instillation to the gastric mucosa significantly increased the net fluxes of sodium and potassium regardless of pre-treatment with cimetidine; 3. the gastric potential difference changes were similar in both the control and the cimetidine-treated groups.

Acknowledgments

Dr. Luiz Nascimento is an Associate Investigator at the VA Medical and Regional Office Center in San Juan, Puerto Rico.

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PRECAUTIONS:

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ADVERSE REACTIONS: The most frequently observed adverse reactions to codeine include light headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation, and pruritus.

The most frequently observed reactions to aspirin include headache, vertigo, ringing in the ears, mental confusion, drowsiness, sweating, thirst, nausea, and vomiting. Occasional patients experience gastric irritation and bleeding with aspirin. Some patients are unable to take salicylates without developing nausea and vomiting. Hypersensitivity may be manifested by a skin rash or even an anaphylactic reaction. With these exceptions, most of the side effects occur after repeated administration of large doses.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. Empirin with Codeine is given orally. The usual adult dose for Empirin with Codeine No. 2 and No. 3 is one or two tablets every four hours as required. The usual adult dose for Empirin with Codeine No. 4 is one tablet every four hours as required.

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Smith GR et al: *Psychosomatics* 15:138, 3rd quarter, 1974

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"The lack of hypotensive effects ... suggests that haloperidol may be preferable to the phenothiazines in the treatment of mental disorders in the aged."

Tobin JM et al: *Geriatrics* 25(6):122, 1970.

"Among the antipsychotic drugs...haloperidol has the lowest anticholinergic potential."

Bernstein JG: *Clinical Psychopharmacology*. Littleton, MA, PSG Publishing Company, 1978, p 123.

Especially useful for treating elderly patients with concomitant diseases

Unlike some of the other major tranquilizers, HALDOL haloperidol may be used concomitantly with other medications frequently prescribed for geriatric patients.

"There really are no drug interactions of major clinical importance involving haloperidol, which is a rather unique advantage of this drug."

Bernstein JG: *Management of Side Effects Related to Antipsychotic Drug Therapy: An Interview*, 1978, p 12

*Although some instances of drowsiness have been reported, marked sedation is rare.

**Transient hypotension occurs rarely; severe orthostatic hypotension has not been reported.

Note: Extrapyramidal symptoms, when they occur, are readily controllable with antiparkinson drugs or dosage adjustment.

Please turn page for summary of prescribing information. Photograph posed by professional model.



concentrate

A tasteless, odorless, colorless
Liquid Concentrate for better
patient acceptability 2 mg per ml
haloperidol (as the lactate).

injection

A rapid-acting injection for psychiatric
emergencies 5 mg haloperidol (as the lactate)
with 1.8 mg methylparaben and 0.2 mg
propylparaben per ml, and lactic acid for pH
adjustment to 3.4 ± 0.2

tablets

5 tablet strengths for convenience in
individualizing dosage

1 mg* 2 mg 5 mg*
1/2 mg 10 mg*

HALDOL[®] (haloperidol)

tablets/concentrate/injection

*contain FD&C Yellow No. 5 (see Precautions)

A dosage form for every therapeutic need

Summary of Prescribing Information

Contraindications: Severe, toxic CNS depression or comatose states from any cause, hypersensitivity to the drug, Parkinson's disease

Warnings: Usage in Pregnancy: Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards. Infants should not be nursed during drug treatment.

Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL haloperidol may block its vasopressor activity and paradoxical further lowering of blood pressure may occur); (2) receiving anticonvulsant medication since HALDOL haloperidol may lower the convulsive threshold; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants. Concomitant antiparkinson medication, if required, may have to be continued after HALDOL haloperidol is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL haloperidol. When HALDOL haloperidol is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL haloperidol. FD&C Yellow No. 5 (tartrazine) may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity

Adverse Reactions: CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug

may have to be discontinued in such cases

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn

Persistent Tardive Dyskinesia: Although rarely reported with HALDOL haloperidol, tardive dyskinesia may appear during or after long-term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and sometimes appear irreversible; there is no known effective treatment and all antipsychotic agents should be discontinued. The syndrome may be masked by reinstitution of drug, increasing dosage, or switching to a different antipsychotic agent.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms

Cardiovascular Effects: Tachycardia and hypotension. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis, agranulocytosis rarely reported and only in association with other medication.

Liver Effects: Impaired liver function and/or jaundice reported

Dermatologic Reactions: Maculopapular and acniform reactions, isolated cases of photosensitivity, loss of hair.

Endocrine Disorders: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia and hypoglycemia

Gastrointestinal Effects: Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Autonomic Reactions: Dry mouth, blurred vision, urinary retention and diaphoresis.

Respiratory Effects: Laryngospasm, bronchospasm and increased depth of respiration.

The injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

Caution: Federal law prohibits dispensing without prescription.

IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

HALDOL tablets and concentrate (120 ml) are manufactured by McNeil Laboratories Co., Dorado, PR 00646

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HAIRY CELL LEUKEMIA CASE REPORT AND REVIEW OF THE LITERATURE

Salomón N. Asmar, MD, Francisco Robert, MD, and
Francisco Muñiz, MD

Summary: Hairy Cell Leukemia is a rare form of leukemia characterized by the presence of bone marrow and reticuloendothelial tissue of mononuclear cells in the peripheral blood. The nature of these cells is unclear and controversy exists as to whether they are lymphocytic or monocytic in origin. Two cases of Hairy Cell Leukemia were studied with immunofluorescent antibody against immunoglobulins, lymphocyte stimulation and erythrocyte rosette formation. In our two patients evidence of a B-lymphocyte origin was found.

Hairy Cell Leukemia (HCL) is a rare condition first described and named Leukemic Reticuloendotheliosis by Ewald in 1923 (1). The disease is characterized by the presence of a large number of atypical, mononuclear cells with large cytoplasmic projections in the bone marrow and blood. These cells usually infiltrate the spleen and occasionally the liver and lymph nodes. On physical examination splenomegaly is an almost universal finding and studies of the peripheral blood show pancytopenia and rarely leukocytosis (2, 3, 4, 5, 6, 7, 8).

As more patients were described, a clear clinical entity was defined, even though, there remained controversy surrounding the nature of the hairy cells (3, 4, 5, 9, 10, 11, 12, 13, 14, 15). These exhibit characteristics usually attributed to lymphocytes (9, 12, 13, 16, 17), but also display phagocytic properties (14, 15) which have led some authors to consider them as monocytes (18).

Here, we report what we believe are the first cases of HCL reported in Puerto Rico and have shown laboratory evidence of their B-lymphocyte origin. Subsequently a review of the literature regarding diagnosis, clinical evolution and therapy is done.

Material and Methods

Surface immunoglobulin anti-immunoglobulin immunofluorescent studies were done by direct technique. Buffy coat smears were thoroughly washed with phosphate buffered saline (PBS) to avoid contamination with circulating immunoglobulin and then separately treated with goat antihuman fluorescent antibody against IgG (heavy and light chains), Mu chain and Alpha chain and incubated for thirty minutes.

Electron microscopy - Electron microscopic sections were fixed with 2.5 percent phosphate buffered glutaraldehyde for two hours; then washed with isotonic PBS and fixed with 1 percent phosphate

From the San Juan VA Medical and Regional Office Center.

Cases presented in the local meeting of the American College of Physicians in Dorado, P. R., October 1978.

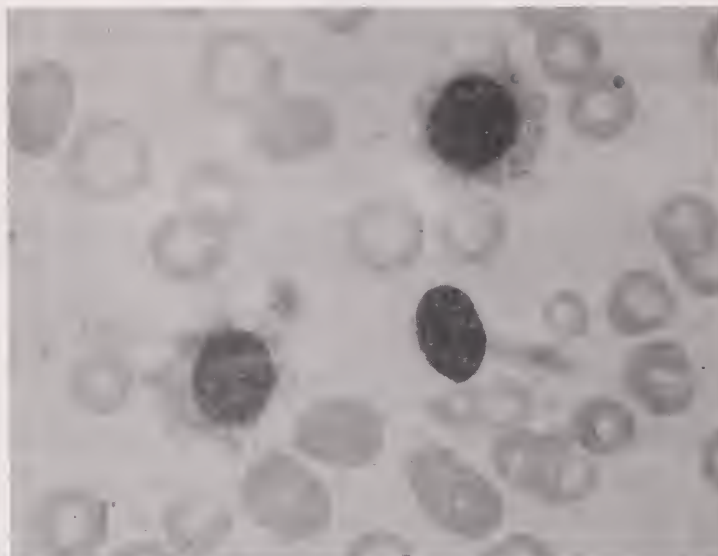


Figure 1: Two of the Typical Hairy Cells are seen in a wright's stain of peripheral smear. Note prominent cytoplasmic projections and normal appearance of back ground cells.

buffered osmium tetroxide (OsO_4) with glucose for one hour at $0-4^\circ \text{C}$. Sections were then washed with isotonic PBS keeping specimen on ice. The cells were dehydrated with acetone 30, 60, 90 and 100 percent solutions and embedded with Epon 812. Thin section for electron microscopic studies was stained with lead citrate and uranylacetate before examination with an RCA-Electron microscope UB-4

Blastic transformation - Cells of the spleen and peripheral blood were isolated with Ficol-Hypaque density fraction and 10^6 cells per cubic millimeter were separated of the A-band. Viability was checked to be at least 90 percent. Cells were cultured using standard lymphocyte transformation techniques in A-B human serum and tissue culture media T-C 199 with small amounts of antibiotics (Penicillin and Streptomycin) then they were incubated at 37°C . in an incubator with 5 percent CO_2 atmosphere.

Peripheral blood and spleen cells were independently stimulated with phytohemagglutinin and

transformation evaluated with tritiated thymidine incorporation measured with a liquid scintillation counter at 3, 5, and 7 days post stimulation.

Case 1:

A 78-year old male was admitted with weakness, pallor, dyspnea and diffuse body pain of 2 months duration. Physical examination showed pallor, hepatomegaly (14 cm. span), splenomegaly (2 cm. below costal margin) and a few enlarged non-tender nodes in left axilla. WBC was $23,600/\text{mm}^3$, HgB- 10gm/dl and platelets - $89,000/\text{mm}^3$. The differential count- 93 percent lymphocytes, 78 polymorphonuclears. There was a predominance of lymphoid cell, most of which displayed bluish cytoplasm with hairy projections, occasional nucleated red blood cells and decreased platelets (Fig. 1). Serum protein electrophoresis and immunoglobulins were within normal limits. Bone Marrow Aspiration was "dry" but a Bone Marrow

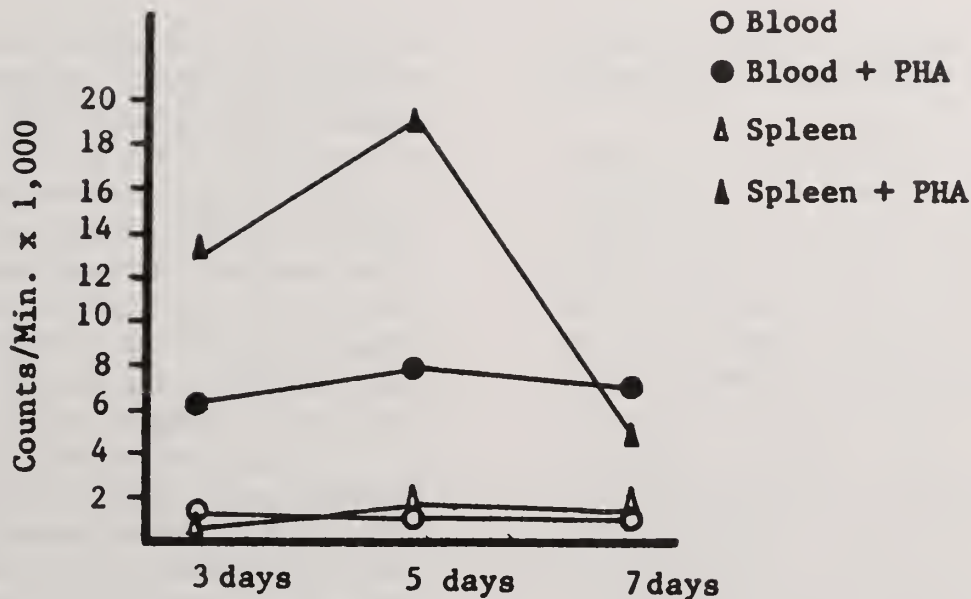


Figure 2: Tritiated thymidine incorporation after PHA stimulation of peripheral mononuclear and spleen cells in Patient II.

Biopsy showed substitution of normal marrow elements by the mononuclear cells with the cytoplasmic projections characteristic of Hairy Cell Leukemia seen in the peripheral smear.

The patient underwent splenectomy and had an uneventful post operative course. Imprints of spleen and peripheral smear were positive for tartrate resistant acid phosphatase. Lymphocyte transformation of peripheral blood and spleen with phytohemagglutinin (Fig. 2) showed increased incorporation of tritiated thymidine by the stimulated cells and negligible incorporation by the non stimulated cells. Electron microscopy showed tall, slender cytoplasmic projections and the presence of cylindric bodies resembling ribosome-lamellae complex. Immunofluorescent studies of the peripheral blood buffy coat using specific antibodies against immunoglobulin were performed. These showed heavy staining along the periphery of the lymphoid cells and their hairy projections, with anti-gamma heavy chain antibody

and slight staining with anti-mu heavy chain antibody.

Since splenectomy the patient has been doing well with peripheral blood counts of 5-10,000/mm³ WBC (70 percent hairy cells) and platelet counts above 100,000/mm³.

Case 2:

A 48-year old male with history of bronchial asthma was hospitalized with chest pain and shortness of breath. He was found to be anemic and was admitted. Physical examination demonstrated a palpable tip of the spleen without hepatomegaly or lymphadenopathy and regular tachycardia. The WBC count was 22,500/mm³ with 97 percent lymphocytes (with hairy projections), 2 percent bands, 1 percent polymorphonuclear, Hgb 11.6 gm/dl and Platelet count of 123,000/mm³. Electrocardiogram-counter clockwise rotation showed no evidence of acute myocardial infarction.

tion. Vectorcardiogram was compatible with posterior wall myocardial infarction. Graded exercise test was negative for ischemic changes.

There was a slight elevation of the Serum IgA 440mg/dl (normal 210-350mg/dl). A Bone Marrow Aspiration showed a cellular marrow with normal elements substituted by mononuclear cells with hairy projections. The granulocytic series and the erythroid precursors were decreased. Megakaryocytes were present with morphologic abnormalities. A Bone Marrow Biopsy showed normal bony trabeculae enclosing marrow. Marrow contained a monotonous lymphoid cell population. Peripheral blood hairy cells were positive for tartrate resistant acid phosphatase stain. Electron microscopy of the marrow showed mononuclear cells with numerous tall, slender cytoplasmic projections, indented nuclei and abundant chromatin. Numerous cytoplasmic mitochondria were present. Immunofluorescence of bone marrow revealed heavy staining of the slender cytoplasmic projections and periphery with anti-gamma antibody and slight staining with anti-mu chain antibody. Study of cellular receptors of the patient's peripheral cells showed 58 percent B and 7 percent T-lymphocytes. The clinical course was plagued with multiple upper-respiratory tract infections and progressive decrease of the platelet count and hemoglobin which finally required splenectomy (five years after diagnosis). He has been doing fairly well since then with peripheral blood counts of 23,100/mm³ WBC (98 percent hairy lymphocytes), Hemoglobin 11.7 gm/dl and platelet count 200,000/mm³.

Discussion

History and Presentation

The clinical characteristics of the disease are well defined (2, 5, 8, 17). These large series reviews will be analyzed and compared with the most prominent findings in our patients.

Patients have a median age of 60 years

and the disease is usually discovered in the 5th, 6th decade, although age range has been from teens to the late eighties in some series. A male to female ratio of 4:1 is usually reported. In close to 1/3 of the cases, symptoms and presenting signs are related to thrombocytopenia and/or recent infection. Incidental discovery of CBC abnormality is the initial finding in close to 40 percent of the cases. About 1/4 of the patients complain of abdominal discomfort which is attributed to splenomegaly.

Our two patients were male, one in the late forties and the other in the late seventies. Patient I presented with constitutional symptoms of anemia and general malaise. Anemia and the striking hairy cells were found incidentally in Patient II. Later in the course of his disease he developed vague abdominal discomfort which was thought to be secondary to his splenomegaly.

Physical Examination

Splenomegaly is found in approximately 80 percent of the cases and it is frequently the only physical finding. The incidence of hepatomegaly has varied from 20-60 percent in different series. Lymphadenopathy is a rare finding and is usually discrete. Only 21 percent of the cases present lymphadenopathy, usually of less than 2 cm. In at least one case, the disease has presented with generalized lymphadenopathy and a lymphoma-like picture (19). Both of our patients presented with splenomegaly. Patient I also had slight hepatomegaly and discrete lymphadenopathy.

Laboratory Findings

The most important findings are those of the peripheral blood smear. Routine chemistry and serum protein electrophoresis usual-

lly give no clue to the diagnosis. In the CBC, hemoglobin levels of less than 12 gm/dl. have been found in 70-75 percent of patients, with about 40 percent between 9-11.9mg/dl. and 30 to 35 percent below 9gm/dl. The leukocyte count varies greatly. More than 40 percent of patients are leukopenic and close to 25 percent exhibit modest leukocytosis. Less than 5 percent of the patients have over 25,000 WBC/mm³. Over 60 percent of patients present significant granulocytopenia of less than 30 polymorphonuclear by 100 cells and lymphocytosis. Monocytopenia has been frequently described (10). In large series (2, 5, 8, 17) it has been shown that approximately 80 percent of the patients have thrombocytopenia (less than 150,000/mm³) at the time of presentation.

The percentage of hairy cells in the peripheral smear varies from being absent to over 75 percent. In occasional cases 100 percent of the circulating white blood cells are "hairy". Unsuccessful bone marrow aspirations are common (10-60 percent reported) in patients with HCL. Successful aspiration and biopsies show heavy infiltration with the mononuclear cells with cytoplasmic projections, usually shorter than those seen in the peripheral blood smear. A differential count of more than 50 percent hairy cells has been considered the "leukemic" phase of the disease (8). These differential counts are usually associated with leukocytosis.

From that standpoint both of our patients were in the leukemic phase with more than 90 percent hairy cells counts and WBC counts above 20,000/mm³. They were both thrombocytopenic and granulocytopenic and with hemoglobin levels below 12 gm/dl. In patient I the aspiration was dry and the cellular findings were documented by bone marrow biopsy (5). Both patients presented the characteristic monotonous mononuclear infiltra-

tion of the hairy cells with substitution of the normal marrow elements.

Special Studies

Electron microscope studies of the HCL have been of interest since the description of ribosome - lamellae complexes in high amounts of hairy cells (4, 9). This finding has been reported in 10-50 percent of patients with HCL, and was clearly shown in our first patient.

Phytohemagglutinin stimulation of hairy cells has been attempted with diverse results. Some reports have shown an uniform maximum response between the third and fifth days (12, 20) in contrast with chronic lymphocytic leukemia cell response which is between the fifth to seventh and normal peripheral lymphocytes response which is maximum in three days (12, 21). Both of our patients showed a maximum DNA synthesis between the third and fifth day after stimulation with phytohemagglutinin.

Positive tartrate resistant acid phosphatase stain of the peripheral blood or spleen tissue has been considered the most characteristic diagnostic stain for the condition in the presence of hairy cells. One of our patients (Patient I) exhibited a strongly positive stain in sections of the spleen.

The results of surface markers studies of the hairy cells have been variable. There are at least two case reports (16, 17) of a T-cell variant as demonstrated by sheep erythrocytes (E') spontaneous rosette formation and only one case report of positive antibody-complement sheep erythrocyte (EAC) formation (15).

Patient II had 57 percent EAC rosette formation and 7 percent spontaneous E rosetting in peripheral blood. Both patients (1) hairy cells had strongly positive anti IgG fluorescence

in the periphery and cytoplasmic projections and minimal anti-mu fluorescent reaction.

Surface immunoglobulin studies of hairy cell have consistently shown the presence of large amounts of immunoglobulin in the cell surface (12-17), and the frequent finding of large percentage of "capping" in hairy cells as compared to chronic lymphocytic leukemia (17).

Management

Management of HCL patients depends on a close clinical and peripheral blood evaluation. There is a general agreement in that splenectomy is the treatment of choice in patients with the leukemic phase of the disease (as described by Catovsky et al (8)) or with symptomatic leukopenia and/or thrombocytopenia. There are also other patients that do well without therapy and should be observed and followed for life.

Chemotherapy in HCL patients has been associated with a poor prognosis and except in very compromised clinical situations its use is not recommended (5, 8, 23, 24, 25). After splenectomy, the percentage of leukemic cells in the peripheral blood is usually not altered although platelet, white blood count and hemoglobin levels tend to rise.

Analysis

Lobuglio in 1976 (11) gave a dramatic description of the condition characterizing it as "a defined syndrome of an ill defined cell".

After the first report by Ewald in 1923, very few publications appeared until 1958, when Bouroncle et al reported twenty six patients characterizing and defining the

clinical features of the disease. Scattered reports appeared until 1969, when new interest in this condition grew stronger.

The most important contribution to the diagnosis of this disease was that of Yam et al in 1971 (25). They found that hairy cells contain a large amount of acid phosphatase-isoenzyme 5, tartrate resistant acid phosphatase. Since this is a relatively unusual finding it has been considered diagnostic of the disease if found in large amounts in the hairy cells.

HCL is almost a medical curiosity, less than 1 percent of the leukemias, but due to its relatively benign course, which can be adversely affected by chemotherapy, the correct diagnosis of the disease is of extreme importance (5, 8). New diagnostic techniques such as the electron microscope demonstration of ribosome lamellae complex by Katayama in 1972 (9) have contributed to the diagnosis.

Rappaport (5), Catovsky (6), and Naeim (17) have recently reported large series of patients which have contributed to the clinical characterization of this disease, but in spite of the new diagnostic tools and clinical knowledge the nature of the mononuclear hairy cells is still the center of heated arguments. It has been demonstrated that surface immunoglobulin is usually associated with a lymphocytic nature. The response of lymphocyte cultures also support a lymphocytic origin, but it has been shown that the cells have phagocytic properties. They have not been shown to phagocytize other cells, material or organisms "in vivo", but exposed to charcoal or candida "in vitro" they have occasionally displayed limited phagocytic properties (14, 15, 26, 27).

All studies performed in our patients point to a B-cell origin of the hairy cells. Probably more sophisticated studies will be needed before the nature of the cells is unequivocally

ascertained.

Summary

Two cases of hairy cell leukemia were diagnosed and studied. Both were treated with splenectomy and are presently doing well. All studies performed suggest a B-cell origin.

Acknowledgments

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DURATION OF ACTION OF AN ANTACID IN TWO GROUPS OF PATIENTS

Luis González, MD and Angel Olazábal, MD

Summary: Gastric emptying of a liquid meal is faster following gastric operations that affect or resect the pyloric sphincter. We evaluated the effectiveness of a single dose of an antacid in subjects who had peptic ulcer disease and who either had a previous vagotomy and pyloroplasty or were unoperated. We report that the duration of action of antacids is shortened in the operated subjects.

Resumen: El vaciamiento del estómago de una comida líquida es más rápido si se ha removido o alterado quirúrgicamente el esfínter pilórico. Hemos evaluado la duración de acción de una dosis de antiácido en pacientes con enfermedad péptica, algunos de ellos con vagotomía y piloroplastía previa. Encontramos que la duración de efecto neutralizante del antiácido es más corta en los pacientes operados.

The emptying of liquids and solids from the gastric lumen into the duodenum is normally a well-controlled physiological process. Neural, hormonal and myogenic mechanisms are involved in regulating gastric emptying (1).

MacGregor et al (2), have documented that gastric emptying of liquids is hastened in patients who had a previous partial gastrectomy or pyloroplasty. Peptic ulcer disease sometimes recurs following gastric operations performed as therapy for active ulcer disease. Patients who have recurrence of peptic disease after a previous gastric operation usually receive antacids orally as therapy. The effectiveness of antacids in this group of patients has not been adequately documented.

We have evaluated the in vivo acid neutralizing capacity of a routine dose of a liquid antacid in subjects who had a previous truncal vagotomy and pyloroplasty performed for peptic ulcer disease and in patients with a previous history of peptic ulcer disease who did not have gastric surgery.

Materials and Methods

Candidates for the study were patients who volunteered to participate and who had: 1) a previous diagnosis of peptic ulcer disease (documented by radiography, endoscopy or surgery); 2) a previous vagotomy and pyloroplasty (V&P) or no previous gastric surgery; 3) an upper gastrointestinal x-ray series performed in the previous month which showed normal or rapid gastric emptying of barium. Each patient provided written informed consent prior to entering the study.

After an overnight fast of at least eight hours, a nasogastric tube was passed into the stomach via the mouth and the stomach emptied by aspiration. The

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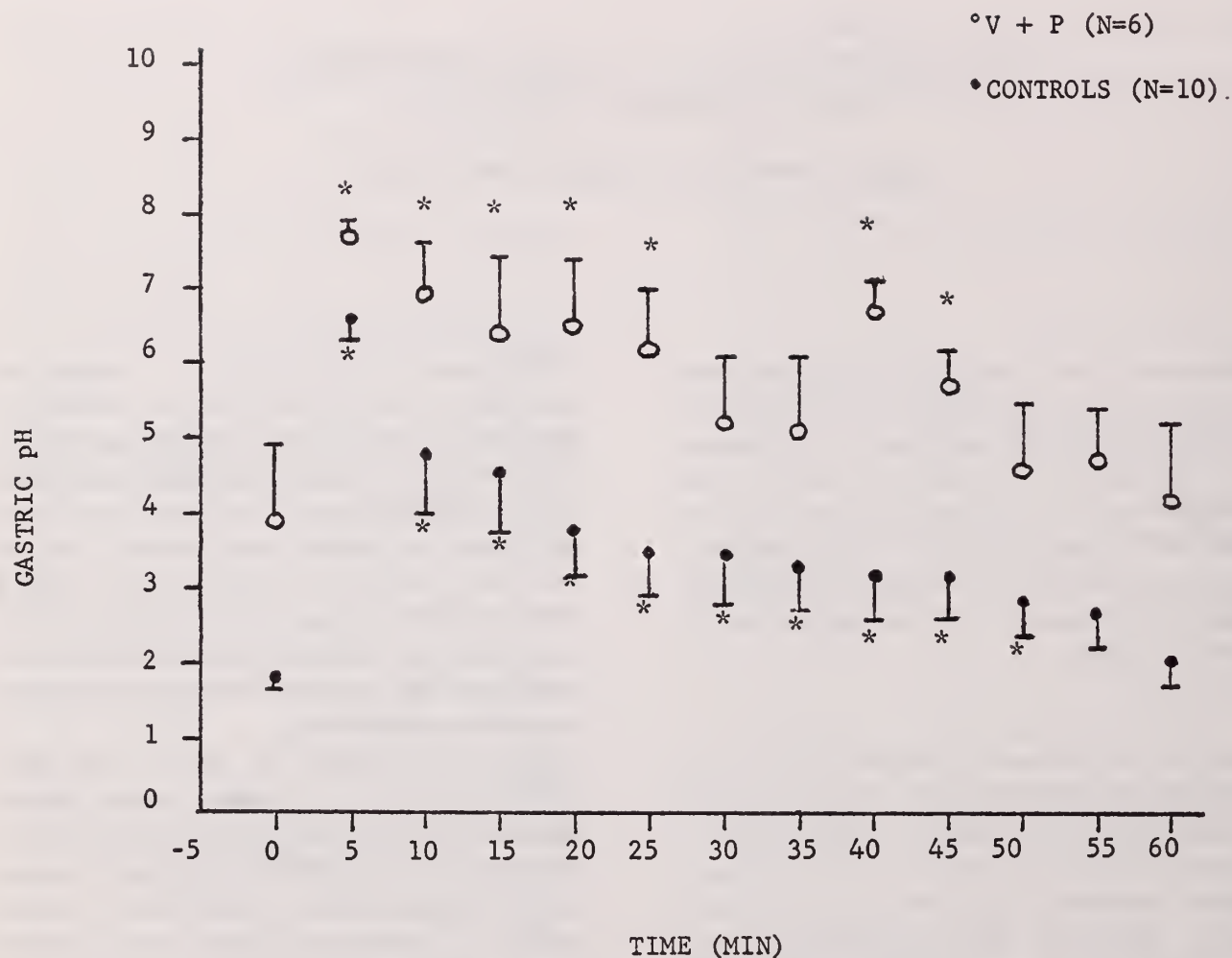


Figure 1: Mean (\pm SEM) values of gastric contents following 30 ml of an antacid (administered at time labeled zero). *indicate values significantly different ($p < 0.05$) from the control pH value (value indicated at time zero).

pH of the gastric secretions was then measured by standard techniques (3) for an hour in 5 ml samples aspirated every 5 minutes. After one hour, 30 ml of Maalox ® was administered to the patient via the gastric tube and the pH of the secretions measured for another hour. The nasogastric tube was removed at the end of this second hour.

The duration of action of the antacid was defined for the purpose of this investigation as the length of time that the pH of the gastric contents stayed above the control pH value. The control pH

value was defined as the mean pH of 5 ml gastric samples taken consecutively every five minutes in the 30 minutes preceding the administration of the antacid.

Student's t-test for unpaired samples was used to determine if a statistical significance existed in the mean duration of action of the antacid in the unoperated patients versus the previously operated patients. Probability values less than 0.05 were considered significant.

Results

All patients included in this study were male. The mean age of the operated group of patients was 49.2 and of the unoperated control group was 45.3 (p value > 0.1). At least one year had elapsed since surgery prior to inclusion in the study. The pH of the gastric luminal contents was significantly more acid in the control group (1.8 vs 3.9).

As shown in Figure 1, following administration of the antacid there was a significant rise in the gastric pH in both groups. In the V & P patients the pH increased from a control value of 3.9 to 7.7 and in the control patients from 1.8 to 6.6. In the unoperated patients the gastric pH remained significantly elevated compared to the control pH value for 50 minutes. In the V & P patients the findings were more complex. In this group the gastric pH remained significantly above the control pH value for 25 minutes only. The pH of the gastric samples at 30 and 35 minutes was not different from the control pH. During the last 15 minutes of the study the pH was not different from the control value.

Discussion

We report that the duration of action of a liquid antacid is decreased following a vagotomy and pyloroplasty. In our V & P patients, the antacid effect lasted 25 minutes as compared to 50 minutes in the unoperated patients. The most likely explanation for the shorter duration of neutralization of gastric acidity in the V & P patients is the shorter stay in the stomach of the antacid. Previous elegant studies by Morton I. Grossman (4) have demonstrated that the rapidity of gastric emptying is probably the most important determinant of the duration of action of an-

tacids. Grossman showed that even though 4 grams of calcium carbonate was enough to neutralize all the gastric acid secreted by an average patient with duodenal ulcer in 27 hours if the reaction was carried out in vitro the effect of 4 grams of calcium carbonate taken by mouth lasted only about forty minutes. He also showed that doubling the standard dose of an antacid does not prolong the neutralization of gastric juice. MacGregor et al (2) recently reported that V & P patients empty about 85 percent of a liquid meal in 1 hour while unoperated controls empty 20 to 25 percent of the meal in the same time period.

We found a higher gastric pH in the operated patients. This was expected. Two factors are probably responsible for this higher pH. One factor is decreased acid secretion. Basal acid secretion is decreased from 60 to 80 percent following a complete truncal vagotomy (5). The second important factor is reflux of the alkaline duodenal contents back into the stomach. Bilirubin was present in the gastric contents at some time during the study in all the V & P patients tested for bilirubin. Although 4 of the 5 unoperated patients tested for bilirubin also had bilirubin in the gastric samples the mean bilirubin concentration was significantly higher in the operated group. We interpret this finding to indicate significantly greater reflux of duodenal contents in the operated patients compared to the unoperated patients.

Recurrence of peptic ulceration has been reported to occur in 4 to 27 percent of patients who have a V & P for peptic ulceration (6, 7). Incomplete vagotomies, gastric stasis, unrecognized Zollinger-Ellison syndrome are some of the causes for recurrence. In a review of this subject by Stabile and Passaro in 1976 (8), they stated that the results of me-

dical treatment had been poor in patients who had recurrent ulceration following V & P. The results of our study strongly suggest that the shorter duration of action of antacids in patients with V & P may be an important factor in the frequent failure of antacid therapy when these patients develop recurrent ulceration associated with persistence of a high acid secretory rate.

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LIVER SCANNING IN THE PRE-OPERATIVE EVALUATION OF THE PATIENTS WITH GYNECOLOGICAL MALIGNANCIES

Samuel Sostre, MD, Edward K. Prokop, MD and
Henry N. Wagner, MD

Summary: One hundred-thirty four liver scans (LS) of patients with known gynecological malignancies were reviewed. Results were compared with the liver function tests (LFT's) to evaluate the relative value of these two parameters in the evaluation of possible liver involvement in these patients.

The LS is believed to be more specific than LFT's in predicting liver involvement by metastases. The LS can separate patients with focal defects from those with non-malignant liver disease in the group of patients with abnormal LFT's. The LS can also detect a small fraction of patients (3 percent) with possible focal liver disease that have normal LFT's and otherwise no indication of hepatic involvement.

Resumen: Ciento treinta y cuatro (134) escintigramas hepáticos de pacientes con malignidades ginecológicas comprobadas fueron repasados. Los resultados fueron comparados con pruebas de función hepáticas séricas para determinar el valor relativo de estos dos pará-

metros en la evaluación de posible envolvimiento hepático en estos pacientes.

El escintigrama hepático es más específico que las pruebas séricas de función hepática en la predicción de envolvimiento hepático por metástasis. El escintigrama puede separar pacientes con lesiones ocupantes de espacio de aquellos con enfermedad hepática no maligna en el grupo de pacientes con pruebas séricas anormales. El escintigrama hepático también puede detectar una fracción pequeña de pacientes (3 por ciento) con posibles lesiones ocupantes de espacio que tienen pruebas séricas normales y ninguna otra indicación clínica de envolvimiento hepático.

One of the major roles played by radioactive tracer techniques such as scanning is the pre-operative assessment of the extent of disease, so that treatment planning can be more rational. In the present study, we have reviewed the results of liver function tests and nuclear imaging in a series of 134 patients with malignancies of the female genital tract in order to answer the following questions: 1) How often are focal defects observed in the liver scan of such patients? 2) How do the findings of the scans compare with chemical evaluation of liver function? 3) What role does liver scanning play in the evaluation of such patients?

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TABLE I

General Statistics

<i>Liver Function Tests</i>	<i>Number of Patients</i>	<i>Focal Defects of Scan</i>	<i>Percent</i>
<i>Normal</i>	<i>97</i>	<i>3</i>	<i>3.1 percent</i>
<i>Abnormal</i>	<i>37</i>	<i>16</i>	<i>43 percent</i>
<i>TOTAL -</i>	<i>134</i>	<i>19</i>	<i>15 percent</i>

Materials and Methods

During a three year period, 299 liver scans were performed in patients referred from the Gynecology Service at the Johns Hopkins Hospital. One hundred and thirty-four patients met the necessary criteria to be included in this study, namely: a) a genital malignancy was present and proven by histology, b) a complete history could be obtained, c) LFT's had been obtained within five days of the date of the liver scan. Patients of all stages were included.

The liver function tests included SGOT, LDH, Alkaline phosphatase and total bilirubin. All were performed on the SMA=12 60 Technikon instrument.

All patients had ten view liver spleen scans (anterior, lateral posterior and oblique views of each organ) approximately 10 minutes after the intravenous administration of 3-5 mCi of ^{99m}Tc -sulfur colloid. An Anger camera with a high resolution parallel hole collimator was used.

The liver scan interpretations used in this report were the official reports given by the Department at the time the study was performed. The scans were classified into two groups: (1) clear-cut focal defects and (2) no focal defects (which includes normal scans and those with non-homogeneous uptake

of the tracer).

Results

Of the 134 cases, 90 had invasive cervical carcinoma (patients with in situ malignancies were not included), 17 had endometrial carcinoma, 12 had miscellaneous pelvic malignancies including a retroperitoneal sarcoma, a tubal malignancy and 3 choriocarcinomas.

Ninety-seven patients (72 percent) had normal LFT's and thirty-seven (28 percent) had abnormal LFT's (elevation of SGOT and/or alkaline phosphatase). Isolated elevation of LDH was not considered a liver function test abnormality. All the patients had a normal serum bilirubin.

Nineteen patients (14.2 percent) had focal defects on the liver scan. Of these 19, sixteen were in the group of patients with abnormal LFT's (43 percent). Only 3 (3.1 percent) were found in the group with normal

TABLE II
Results of Liver Scans and Liver Function Tests Determination

Disease	Normal Liver Function Tests		Abnormal Liver Function Tests		Total
	Normal Scan	Scan with Focal Defects	Normal Scan	Scan with Focal Defects	
<i>Carcinoma of Cervix 1</i>	24	---	2	3 (1)	29
<i>Carcinoma of Cervix 2</i>	21	2	2	2 (1)	27
<i>Carcinoma of Cervix 3</i>	7	---	5	---	12
<i>Carcinoma of Cervix 4</i>	4	1	1	---	6
<i>Carcinoma of Cervix undetermined stage</i>	13	---	3 (1)	---	16
<i>Vagina and Vulva</i>	6	---	3	1	10
<i>Ovaries</i>	6	---	3 (2)	3	12
<i>Endometrium</i>	9	---	1 (1)	7	17
<i>Others</i>	4	---	1	---	5
TOTAL	94	3	21	16	134

(1) Number in parentheses represents number of patients with isolated SGOT elevation and normal Alkaline Phosphatase Levels.

LFT's. (Tables I and II).

Tables III and IV show the incidence of focal defects in the liver scans in patients divided by disease categories and by LFT's.

Discussion

The accurate diagnosis of hepatic metastases in patients with known genital malignancies is very important since the type of

therapy undertaken may be drastically altered. However, this diagnosis is not simple, short of laparotomy.

To evaluate patients with known genital malignancies for liver metastases, liver function tests (LFT's) and liver scans are routinely performed in some medical centers. Both tests have their advantages and limitations. In general, the alkaline phosphatase level is very sensitive, being abnormal in 80-90 percent of

TABLE III

Total Incidence of Focal Defects Divided by Disease Category

<i>Disease</i>	<i>Number of Patients</i>	<i>Focal Defects on Scan</i>	<i>Percent</i>
<i>Carcinoma of Cervix</i>	90	8	9 percent
<i>Carcinoma of Vulva</i>	10	1	10 percent
<i>Carcinoma of Ovaries</i>	12	3	25 percent
<i>Carcinoma of Endometrium</i>	17	7	41 percent

TABLE IV

Incidence of Focal Defects in Patients with Abnormal LFT's Divided by Disease Category

<i>Disease</i>	<i>Number of Patients</i>	<i>Focal Defects on Scan</i>	<i>Percent</i>
<i>Carcinoma of Cervix</i>	18	5	28 percent
<i>Carcinoma of Vulva</i>	4	1	25 percent
<i>Carcinoma of Ovaries</i>	6	3	50 percent
<i>Carcinoma of Endometrium</i>	8	7	87.5 percent

cases with hepatic metastases (1-4). However, it has a low specificity (48 percent) as it may be abnormal in any type of liver disease, in patients with bony metastases or in certain benign and malignant disorders of the gastrointestinal system in the absence of hepatic involvement (1, 3-6).

The liver scan on the other hand is very specific (90 percent) but its sensitivity is lower, detecting approximately 70-78 percent of hepatic lesions (3-5).

As 10-20 percent of patients with hepatic metastases will be missed by the alkaline phosphatase determination, where as

20-25 percent will be missed by liver scanning it is intuitively derived that the number of patients with a normal alkaline phosphatase level that will have focal defects on the liver scan should be low. In our series only 3 percent of the patients with normal LFT's had focal defects on the liver scan.

This finding suggests that, at least for genital malignancies, in 97 percent of the cases (but not in all) a hepatic lesion that is too small to cause elevation of the LFT's is also too small to appear on the liver scan.

On the other hand, in 3 percent of patients in which metastases were not suspected otherwise, the liver scan detected focal defects.

In our series, 37 patients (28 percent) with genital malignancies had abnormal LFT's (elevation of SGOT and/or alkaline phosphatase). Of these, 16 (43 percent) had focal disease on the liver scan.

Liver scanning is a useful screening procedure in patients with gynecological cancers and has two major roles in this setting: (1) it adds specificity to the LFT's and separates patients with focal defects from those with non-malignant liver disease in the group with an elevated SGOT and/or alkaline phosphatase. Focal disease will be present in about half of these patients. 2) It can detect a small fraction of patients (3-4 percent) with possible liver disease that have normal LFT's and otherwise, no indication of hepatic involvement.

Focal disease of course, is not pathognomic of metastases. Cysts, hemangiomas and pseudotumors, among others, usually present

a similar focal pattern. However, the presence of focal hepatic disease in the appropriate setting makes the diagnosis of metastases to the liver highly probable, with a specificity of 90 percent.

One must keep in mind that management decisions can not be made on the basis of a single study (i.e. liver scan) and that the entire clinical picture must be taken into account before a treatment regimen is instituted.

Today we count with other non-invasive techniques, such as ultrasound and computerized tomography, which can augment the specificity of the liver scan findings. However scintigraphy remains the method of choice for the initial evaluation of the patient with suspected metastases to the liver.

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COMUNICACIONES LIBRES

Puerto Rico, gracias a su clima y localización geográfica, goza de un gran número de reuniones médico-científicas. En la gran mayoría de ellas los temas son escogidos por su valor práctico y son discutidos en paneles, mesas redondas y comunicaciones libres. En dos foros se ha tenido la oportunidad de presentar y discutir trabajos originales de investigación: la asamblea anual de la Asociación Médica de Puerto Rico y la reunión anual del Colegio Americano de Médicos (American College of Physicians). Aunque la calidad de estas sesiones usualmente es excelente, la asistencia ha sido, en términos generales, pobre. Se ha asumido que el médico es atraído más por simposios que por sesiones de comunicaciones libres y esto ha llevado a organizadores de programas a reducir gravemente los espacios para comunicaciones libres en estas reuniones. Esta tendencia, si se lleva al extremo, puede ser un arma de doble filo. Las comunicaciones libres tienen una gran importancia. Primero, sirven como un medio de comunicación para familiarizar a la comunidad médica con el trabajo de los investigadores locales. Segundo, estas reuniones sirven de foro para la discusión y análisis crítico de estos trabajos. Estos aspectos educativos son de vital importancia en el desarrollo de la actitud científica y analítica que debe tener todo médico, especialmente en vista de la tecnología que se ha desarrollado en los últimos 15 años. Tercero, las sesiones sirven como estímulo para investigadores jóvenes, internos y residentes ya que se les brinda una tribuna donde pueden exponer sus experiencias. Cuarto, las sesiones libres sirven a manera de entrenamiento o de "ligas menores" para que los investigadores puedan pulir sus técnicas de diseño, presentación y discusión en trabajos científicos. Varios trabajos locales presentados en estas reuniones han generado presentaciones nacionales e internacionales subsiguientemente. Quinto, los abstractos de los trabajos presentados en estas reuniones han servido como material científico para publicación en este Boletín sirviendo así de documento permanente sobre los esfuerzos individuales de nuestra clase médica en la investigación.

Es muy posible que al sustituir las sesiones de comunicaciones libres con paneles y simposios aumente el interés general y la asistencia, pero no nos olvidemos que podríamos perder todos los beneficios aliados a las sesiones libres si éstas se eliminasen por completo. No permitamos que el afán por los números y la asistencia extinga la luz que difunde la investigación.

Guillermo Cintrón, MD, FACP

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related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg (white, scored), 50 mg (aqua) in bottles of 100, 1000 and 5000, 25 mg (peach) in bottles of 100 and 1000, unit-dose blister packs, boxes of 100 (10 x 10 strips).

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AVISO DE INTERES

La Junta Editora, consciente de su responsabilidad de hacer que el "Boletín" cumpla a cabalidad con su cometido de divulgar conocimientos médicos, elevar las normas de educación médica y al propio tiempo de llenar las necesidades de todos los compañeros médicos, ha acordado establecer una nueva Sección que se conocerá como "Sección de Preguntas".

Bajo esta nueva Sección, todos los compañeros tendrán la oportunidad de enviarnos preguntas médicas de casos difíciles o casos clínicos para opinión experta. Estas preguntas, con sus respuestas, serán publicadas en esta nueva Sección.

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Other major contraindications to the use of bethanechol chloride are latent or active asthma, pregnancy, hyperthyroidism, and coronary occlusion. Additional contraindications are bradycardia, atrio-ventricular conduction defects, vasomotor instability, hypotension, hypertension, coronary artery disease, epilepsy, and parkinsonism.

Precautions: Special care and consideration are required when bethanechol chloride is administered to patients concomitantly being treated with other drugs with which pharmacologic interactions may occur. Examples of drugs with potentials for such interactions are: quinidine and procainamide, which may antagonize cholinergic effects; cholinergic drugs, particularly cholinesterase inhibitors, where additive effects may occur. When administered to patients receiving ganglionic blocking compounds a critical fall in blood pressure may occur which usually is preceded by severe abdominal symptoms.

In urinary retention, if the sphincter fails to relax as Duvoid (bethanechol chloride) contracts the bladder, urine may be forced up the ureter into the kidney pelvis. If there is bacteriuria, this may cause a reflux infection.

Adverse Reactions: Untoward effects are usually due to overdosage but occur infrequently with the oral administration of bethanechol chloride. Abdominal discomfort, salivation, flushing of the skin ("hot feeling"), sweating, nausea and vomiting are early signs of overdosage. Asthmatic attacks, especially in asthmatic individuals, may be precipitated. Substernal pressure or pain may occur, however, it is uncertain whether this is due to bronchoconstriction, or spasm of the esophagus. Myocardial hypoxia must be considered if a marked fall in blood pressure occurs.

Transient syncope with cardiac arrest, transient complete heart block, dyspnea, and orthostatic hypotension may be associated with large doses. Patients with hypertension may react to the drug with a precipitous fall in blood pressure. Short periods of atrial fibrillation have been observed in hyperthyroid individuals following the administration of cholinergic drugs. Also, involuntary defecation and urinary urgency may occur after large doses.

Atropine sulfate is a specific antidote. A dose of 0.6 mg-1.2 mg (1/100 grain-1/50 grain), for intramuscular or intravenous administration should be readily available to counteract severe toxic cardiovascular or bronchoconstrictor responses to bethanechol chloride.

Dosage and Administration: Dosage must be individualized, depending on type and severity of the conditions to be treated.

The usual adult oral dose is administered with 10-mg, 25-mg, and 50-mg tablets 2, 3, or 4 times daily up to a maximum dosage of 120 mg. The minimum effective dose is determined by giving 10 mg initially, and repeating with 25 mg, and then 50 mg at six hour intervals, until the desired response is obtained. The drug's effects appear within 60 to 90 minutes and persist for up to six hours. Individual doses should, therefore, be spaced at least six hours apart.

How Supplied: Duvoid (bethanechol chloride) is available in: 10-mg pale orange tablets (coded "Eaton 045"), supplied in Unit-of-Use bottles of 100 and unit dose 100's; 25-mg white tablets (coded "Eaton 046"), supplied in Unit-of-Use bottles of 100 and unit dose 100's; 50-mg tan tablets (coded "Eaton 047"), supplied in Unit-of-Use bottles of 100 and unit dose 100's.

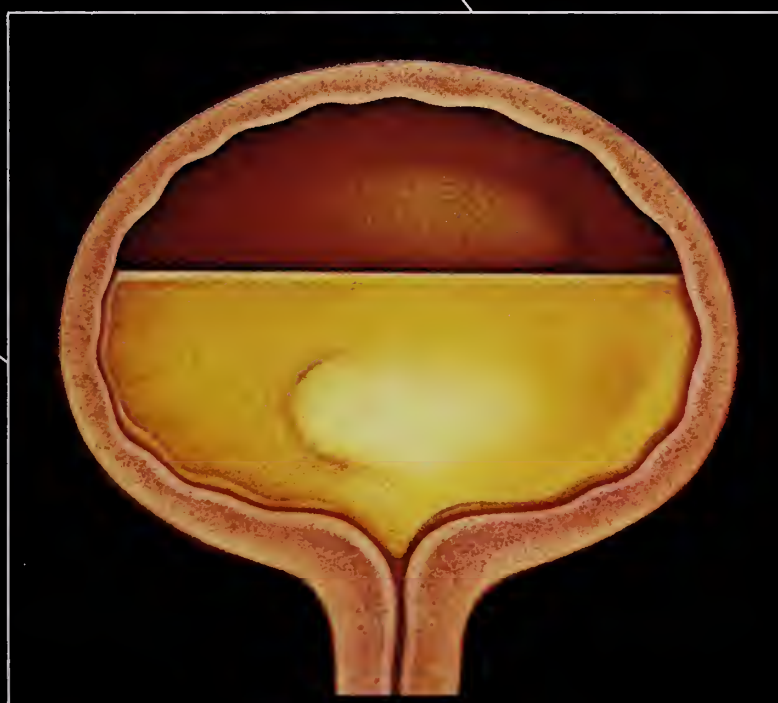
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See previous page for brief summary of prescribing information.

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Adverse Reactions Transient symptoms of abdominal pain and diarrhea have occurred in cases of massive infection and expulsion of worms.

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* Mean cure rate of VERMOX[®] in treating whipworm; cure rate range of 61-75%. Data on file at Janssen Pharmaceutica Inc.

** Mean egg reduction of VERMOX[®] in treating whipworm; egg reduction range of 70-99%. Data on file at Janssen Pharmaceutica Inc.

† Rollo, I.M.: Drugs used in the chemotherapy of helminthiasis, in Goodman, L.S.; and Gilman, A. (eds.): *The Pharmacological Basis of Therapeutics*, ed. 5. New York, Macmillan, 1975, p. 1034.

†† Miller, M.J.; Krupp, I.M.; Little, M.D.; Santos, C.: Mebendazole an effective anthelmintic for trichuriasis and enterobiasis. *JAMA* 230 (10): 1412-1414, Dec. 9, 1974.

1. Registered trademark of Merck Sharp and Dohme.
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DETERMINATION OF AMPUTATION LEVEL MEASUREMENT OF SKIN BLOOD FLOW WITH XENON Xe 133

Wesley S. Moore, MD, San Francisco

En 31 pacientes que se iban a someter 33 amputaciones debajo de la rodilla, el flujo de sangre de la piel adyacente a la línea anterior de incisión fue medida con Xenon Xe 133 en un intento de correlacionar el éxito en la cicatrización con la cantidad de flujo sanguíneo en la piel. Tres amputaciones no cicatrizaron debido a necrosis isquémica. Estas tres amputaciones tenían los niveles más bajos de flujo sanguíneo, indicando que el uso de este método en la piel, es un método prometedor para la selección preoperatoria del nivel de amputación. Una comparación del flujo sanguíneo en la piel con el nivel de pulsos distales palpables y la data angiográfica de la circulación periférica demostraron no tener correlación, confirmando que estas medidas para estimación cualitativa del flujo sanguíneo no debe ser usada en la selección del nivel de amputación.

(Sometido por Rafael Seín, MD)

LOW BACK PAIN OF THORACO LUMBAR ORIGIN.

Maine R.: *Arch Phys Med Rehabil* 61: 389-395, 1980.

El dolor de la espalda baja proveniente de las articulaciones apofisarias de la región toraco-lumbar es muy común y es, erróneamente atribuido, a cambios

patológicos en la espalda baja. El diagnóstico de esta condición es puramente clínico. Los signos clásicos son: prueba positiva del punto en la cresta ilíaca, prueba de doblar la piel positiva, dolor localizado sobre ciertos procesos espinosos en la columna toraco-lumbar y dolor sobre la articulación apofisaria envuelta. El diagnóstico se confirma por bloqueo local periapofiseo en la articulación envuelta. De una serie de 350 pacientes 40 por ciento tenían dolor toraco-lumbar. El tratamiento incluyó manipulación, infiltración con corticoesteroides, electrocoagulación y/o denervación quirúrgica de la articulación envuelta.

(Sometido por Jesús A. Maldonado, MD)

PIOGENIC ARTHRITIS OF THE SHOULDER OF THE ADULT - ARTRITIS PIOGENICA DEL HOMBRO DEL ADULTO

Richard H. Gelberman, MD, Robert B. Winter, MD, Lowell Lutter, MD, J. Bone Joint Surgery, pp. 550-553, June 1980 62-A/4.

Se evaluaron 15 pacientes con 16 articulaciones glenohomerales sépticas. En cada uno de los pacientes había por lo menos un factor predisponente. Cada paciente se sometió a uno de dos tratamientos: aspiraciones repetidas (once hombros) o artrotomía (cinco hombros), combinados con antibióticos parenterales. Los factores más significativos responsables de un tratamiento con pobres resultados fueron el retraso en la instauración de la terapia, la virulencia del organismo causal y la presencia de un proceso patológico subyacente. En ocho de diez hombros en los cuales el tratamiento se instauró cuatro semanas o menos después del comienzo de los síntomas,

se obtuvo un resultado funcional satisfactorio, mientras que todos los seis pacientes que recibieron tratamiento luego de un retraso de más de 4 semanas obtuvieron pobres resultados.

Los seis pacientes infectados con *Estreptococo* o *Estafilococo* coagulasa-negativo obtuvieron resultados satisfactorios. Dos de los ocho pacientes con *Estafilococo aureus* u organismos gram negativos tuvieron resultados satisfactorios; no fue así para los restantes seis.

Los dos pacientes tratados exitosamente por *Estafilococo aureus* fueron diagnosticados tres días después de la aparición de los síntomas mientras que en los otros se retrasó la instauración del tratamiento.

(Sometido por Miguel Angel Berríos, MD)

RELACION ENTRE EL SINDROME DE DOLOR DE ESPALDA Y HALLAZGOS RADIOLOGICOS (ESPINA BIFIDA OCULTA)

Alexander Magora, Armin Schwartz, Scan. J. Rehab. Med., Vol. 12, pp. 9-15

La relación entre el Síndrome de dolor de espalda y la espina bífida oculta se estudió tomando 1244 sujetos, de los cuales 800 tenían dolor de espalda y 44 sirvieron de control. Se compararon: sexo, edad, características ocupacionales, curvaturas en la columna vertebral, movimientos de la columna e historia laboral. Se concluyó que la espina bífida oculta no juega un papel etiológico, no causa predisposición al dolor de espalda ni tiene influencia en su cronicidad.

La data obtenida sugiere que la severidad del dolor de espalda puede aumentar con la espina bífida oculta.

(Sometido por Miguel Angel Berríos, MD)

THE FROZEN SHOULDERS: A REVIEW OF MANIPULATIVE TREATMENT

Thomas, D, Williams, R. A., and Smith, D. S.: Rheumatology and Rehabilitation, 1980, 19, 173-179.

La patogénesis y el manejo de "frozen shoulder" sigue siendo controversial. Un repaso de la literatura sugiere que capsulitis constrictiva es un rasgo patológico común a casos crónicos y esto provee lo racional para el tratamiento manipulativo.

Treinta pacientes con "frozen shoulder" fueron localizados al azar en dos grupos de tratamiento. Un grupo recibió manipulación e inyección local con esteroides solamente. Una evaluación al mes demostró muy poca diferencia entre un grupo y otro. A los tres meses el grupo tratado con manipulación e inyección de esteroides demostró gran mejoría en el arco de movimiento (40 por ciento), comparado al grupo que recibió la inyección solamente (13 por ciento). El grupo manipulado también demostró mejoría substancial en los niveles de dolor diario comparado a aquellos que solo recibieron la inyección (47 por ciento), y su incapacidad se resolvió en 47 por ciento comparado al grupo de solo la inyección donde únicamente el 13 por ciento no tuvo incapacidad.

El número de pacientes es muy pequeño en este estudio para que los resultados sean significativos estadísticamente, pero las tendencias que se demuestran son consistentes con otras series similares y sugiere que esta forma de tratamiento es lógico y efectivo.

(Sometido por Rafael Alvarez, MD)

ACUTE INTERSTITIAL NEPHRITIS RELATED TO CIMETIDINE THERAPY

W. R. McGowan and S. E. Vermillion. Gastroenterology 79: 746-749, 1980

Los autores reportan el primer caso de nefritis intersticial comprobado con biopsia renal asociado al uso de cimetidina (Tagament®). Dos semanas después de comenzar a usar cimetidina el paciente desarrolló fiebre, anorexia y mialgia generalizada asociado con leucocitosis, eosinofilia, piuria estéril y disfunción renal. La función renal y el estado clínico del paciente mejoraron dos semanas después de descontinuar cimetidina. Cuatro meses más tarde la función renal era normal. Los autores piensan que hubo una relación de hipersensitividad asociada al uso de cimetidina y alertaron a los médicos que prescriben la droga de esta posible reacción adversa.

(Sometido por Angel A. Olazábal, MD)

CORRELATION BETWEEN ANTI-RANA AND ANTI-EBNA TITERS IN NORMAL SUBJECTS WITH AND WITHOUT HLA-DRw4

Michael A. Catalano, Dennis A. Carson, Peter Stastny, Sofia Freer, and John H. Vaughan - Clinical Research Department, La Jolla, CA. *Arthritis and Rheumatism*, Vol. 23, No. 9 (September 1980)

We have determined the relationship of antibody titers to the rheumatoid arthritis nuclear antigen (RANA) and of antibody titers to the Epstein-Barr virus alloantigen in the sera of 34 normal white adults. By a sensitive indirect immunofluorescence (IF) assay, 76 percent had RANA antibody, compared to 23 percent by a micro-immunodiffusion assay. The correlation coefficient for the tube dilution titers of anti-RANA and anti-EBNA was 0.61 ($P = 10^{-4}$). The 14 DRw4-positive subjects and the 20 DRw4-negative subjects did not differ with respect to anti-RANA titers ($P = 0.51$) or anti-EBNA titer ($P = 0.89$). We conclude that: 1) most normal adults have RANA antibody by IF; 2) anti-RANA and anti-EBNA titers are closely related; 3) the titers of these antibodies cannot be related to the presence of the DRw4 determinant in normal persons.

(Submitted by Edwin Mejías, MD)

AJUSTE SEXUAL EN EL AMPUTADO DE LA EXTREMIDAD INFERIOR

Leon Reinstein, MD, Judy Ashley, MSW, Kathleen Haas Miller, BA - *Arch Phys Med Rehab* Vol 59: 501-504, 1978.

El ajuste sexual de amputados de la extremidad inferior fue evaluado entrevistando 60 adultos con amputaciones recientes, 39 hombres y 21 mujeres, después de hacerse independientes en la ambulación con su prótesis. Entre los hombres 77 por ciento refirieron una disminución significativa en la frecuencia del acto sexual después de la amputación, mientras que solo 38 por ciento de las mujeres refirieron disminución. La frecuencia de disminución fue mayor en los hombres solteros que en los casados, mayor en los hombres con amputación por encima de la rodilla, y mayor en los hombres en los cuales el fenómeno de "phantom" persistía, comparados con los que ya no existía. La disminución de la frecuencia de relaciones sexuales en los hombres amputados no estaba relacionada con la edad, educación u etiología de la amputación. No hubo ningún cambio significativo en otros aspectos de la actividad sexual incluyendo relaciones oro-genitales, masturbación, homosexualidad y relaciones extra-maritales.

(Sometido por Rafael Seín, MD)

CANCER REHABILITATION: ASSESSMENT OF NEED, DEVELOPMENT AND EVALUATION OF A MODEL OF CARE

Lehmann, JF, De Lisa JA, Warren CG, de Lateur BJ, Bryant, PLS, Nicholson, CG - *Arch Phys Med Rehab* Vol 59: 410-419, 1978.

Una muestra de 805 pacientes con cáncer, comparable pero no idéntico con un estudio nacional, fue analizado para identificar los problemas de rehabilitación encontrados en las distintas localizaciones del cáncer, la necesidad de servicios de rehabilitación y los lapsos en dar el servicio de rehabilitación. Un número significativo de problemas fueron encontrados que po-

dían mejorar con un programa de rehabilitación. Problemas psicológicos fueron usualmente encontrados y aparentan ser más severos en pacientes con impedimentos físicos; estos pacientes tienen que hacer ajustes tanto para una enfermedad mortal y para una condición de impedimento físico. Estos hallazgos demuestran la necesidad de tener en el servicio de oncología los servicios de psicología, y también cuando el cáncer esté asociado con un impedimento físico significativo tener un equipo de rehabilitación con capacidad de manejo psicológico. Las barreras primarias que evitan llevar a cabo un buen programa de rehabilitación son la falta de identificación de los problemas del paciente y/o la falta del referido debido a médicos no familiarizados con el concepto de rehabilitación. Los gastos del cuidado médico fueron costeados por seguros privados, Medicare y Medicaid; la ayuda económica por parte de la familia del paciente contribuyó, aún en los estadios avanzados. Un modelo de rehabilitación fue establecido e implantado con el resultado de que las fallas y barreras para hacer llegar el servicio de rehabilitación desaparecieron.

(Sometido por Rafael Seín, MD)

MOBILIZING A FROZEN SHOULDER

Frederick Lee Liebott, Resident and Staff Physician Vol 26: 8, 64-65.

Artículo corto, descriptivo, acompañado de fotografías de cuatro maniobras para la corrección del hombro anquilosado.

En el síndrome del hombro anquilosado el dolor se produce por la limitación de la coyuntura en sí, y no por la bursitis que usualmente origina el proceso. Esto se puede comprobar mediante el hecho que en un hombro anquilosado el dolor agudo se produce al final del movimiento restringido, mientras que en una bursitis hay movimiento completo pasivo sin dolor. Las cuatro maniobras son del tipo de ejercicios pasivos

y deben ser dados bajo la supervisión del médico o terapeuta físico.

(Sometido por José A. Arabía, MD)

INSTRUCTING PATIENTS IN PHYSIOTHERAPY: AN EXAMPLE USING THREE METHODS

V. Wright, R. Hopkins and M. Jackson - Rheumatology and Rehabilitation Vol. 19: 91-99, 1980.

Artículo cuyo propósito es determinar la forma más efectiva de dar directrices fisioterapéuticas al paciente. Utiliza 52 pacientes con artritis reumatoidea de las manos que fueron instruidos por tres medios diferentes en el uso del baño de parafina y ejercicios para las manos en la casa. Se determinó que la forma más efectiva de comunicación fue la de instruir al paciente en el salón de terapia mediante demostración una sola vez. La menos efectiva fue la de darle al paciente instrucciones por escrito sin demostración. También se determinó que el dar más de una sesión de demostración no aumentaba significativamente la comprensión de la terapia. Esto es, que basta con una sola demostración de la terapia a seguir.

(Sometido por José Antonio Arabía, MD)

SEMIMEMBRANOUS TENOSYNOVITIS

N. Halperin, A. Axer - Orthopedic Review, July 1980 pp 72-75

Artículo que presenta la experiencia con el tratamiento conservador de la tenosinovitis del mús-

culo semimembranoso en 172 pacientes.

El artículo concluye que se obtuvo buen resultado en la mayoría de los pacientes y propone un tratamiento inicial con analgésicos y ultrasonido luego del cual si no hay mejoría se infiltra una solución de cortisona y anestésico local. En total 87 por ciento de la serie mejoró con analgésicos, fisioterapia e infiltración de cortisona.

Los casos más recalcitrantes fueron aquellos en que había osteoartritis o tendinitis de pes-anserinus (inserción conjunta del gracilis semimembranoso y semitendinoso) concomitantemente con la tenosinovitis del semimembranoso pero aún así muchos de estos mejoraron con infiltración de cortisona.

El artículo también discute la etiología de la tenosinovitis.

(Sometido por J. A. Arabía, MD)

ILIOLUMBAR SYNDROME AS A COMMON CAUSE OF LOW BACK PAIN: DIAGNOSIS AND PROGNOSIS

G. G. Hirschberg, MD, L. Froetscher, MD, F. Naeim, MD - *Arch Phys Med Rehabil Vol 60 - September 1979 - pp 415 - 419*

La mayoría de los casos de dolor de espalda baja caen en la categoría de no específico, en los cuales no puede detectarse patología por rayos X, pruebas de laboratorio o biopsia. Según la experiencia de los autores, aproximadamente el 50 por ciento de los pacientes que caen en la categoría mencionada, tienen un cuadro clínico caracterizado por síntomas y signos localizados en una cresta ilíaca. Los síntomas pueden abolirse temporalmente mediante la infiltración de la cresta ilíaca posterior con lidocaína. Dada la localización de los síntomas y la etiología desconocida, se sugiere el término de síndrome iliolumbar. Una distinción entre síndrome iliolumbar y síndrome de irritación radicular puede evitar cirugía innecesaria. El síndrome iliolumbar crónico es una causa frecuente

de incapacidad por dolor de espalda bajo, lo cual es un factor que no se reconoce frecuentemente.

(Sometido por Miguel A Berrios, MD)

BREAST PAIN, SYMPTOM OF CERVICAL RADICULOPATHY

La Ban MM, Meerschaert, JR, Taylor, RS - *Arch Phys Med Rehab Vol 60: 315-317, 1979*

Dieciocho pacientes femeninas las cuales tenían extensas evaluaciones no informativas de las glándulas mamarias, incluyendo mamogramas y biopsias, fueron tratadas con éxito con tracción cervical debido a dolor crónico en el área torácica de la glándula mamaria. Cada paciente presentaba evidencia clara, clínica o electromiográfica de compromiso de raíz nerviosa cervical. Quince de ellas presentaron evidencia de espondilosis a nivel C-6, C-7. Angina cervical, consistente en un grupo de síntomas producidos por radiculopatía cervical y semejando enfermedad coronaria esquémica, es una entidad bien definida. Menos reconocido que ésta es el dolor persistente de glándula mamaria como síntoma de presentación de envolvimiento radicular cervical. En ambas instancias, la identificación temprana ayuda a aminorar el efecto físico y psicológico del paciente ya que el pronóstico e implicaciones terapéuticas son completamente diferentes. Se describe el mecanismo de producción de dolor y el patrón anatómico de referencia.

(Sometido por Jesús A. Maldonado, MD)

ARTHROGRAPHY - ASSISTED INTRA-ARTICULAR INJECTION OF STEROIDS IN TREATMENT OF ADHESIVE CAPSULITIS

Joseph J. Weiss, MD, Ming Ting, Y., MD - *Arch Phys Med Rehab Vol 59: 285-287 June 1978*

Una vez establecido el diagnóstico de capsulitis adhesiva mediante artrografía del hombro, se procede a inyectar esteroides a través de la aguja "in situ" del artroscopio. Subsiguientes inyecciones intra-articulares de esteroides, si fueron necesarias, se dieron en la clínica externa utilizando el mismo sitio establecido cuando se hizo la artrografía. De un total de 18 pacientes tratados de esta forma, 16 obtuvieron recuperación funcional suficiente para poder volver al trabajo usual y sus actividades del diario vivir. En 11 pacientes, la mejoría estuvo asociada con un movimiento indoloro completo del hombro. Esta terapia aparenta ser preferida a otras formas de inyección intra-articular y es una alternativa a la cirugía cuando la terapia física ha fallado.

(Sometido por Rafael Aguayo, MD)

THE TREATMENT OF PERSISTENT SYNOVITIS WITH NITROGEN MUSTARD

Jones, JG, Lewis P, Hazelman BL - Rheumatology and Rehabilitation Vol 19: 154-160, 1980

La mostaza nitrogenada intra-articular se usa muy poco en el presente. Los efectos secundarios y el asumir que los pobres resultados obtenidos con thiotepa (un producto relacionado) aplican a la mostaza nitrogenada, parecen ser las razones principales. Este estudio retrospectivo trata de determinar si la mostaza nitrogenada se descartó prematuramente.

Se inyectó mostaza nitrogenada en 44 rodillas de 33 pacientes. Un resultado excelente se obtuvo en 24 articulaciones (sin recurrir el dolor ni la efusión en un año) y algo de dolor y efusión se observó en otras nueve articulaciones. Los desagradables efectos secundarios iniciales como náusea, vómitos, pirexia y dolor local pronto desaparecieron.

Mostaza nitrogenada parece producir un efecto beneficioso en sinovitis crónica, pero los efectos secundarios sistémicos siguen siendo una desventaja. Este tratamiento sería más aceptable si la droga permaneciera dentro de la articulación. Mostaza nitrogenada

entrampada dentro de liposomas podría proveer un método satisfactorio de suplirla.

(Sometido por Rafael Alvarez, MD)

PARAPLEGIA DURING SKIN DIVING (13 CASES)

R. Girard, Paraplegia Vol 18: 123-126, 1980

Estudio que repasa trece casos de paraplejía luego de haber buceado a unas profundidades de 30-40 metros, doce hombres, una mujer, todos con experiencia en bucear a profundidades, entre las edades de 27-50 años. Estuvieron sumergidos por 15-30 minutos y el ascenso fue con paradas de compresión en algunos y otros no.

La sintomatología fue de origen súbito, usualmente en el área posterior torácica. Cuatro se sintieron mareados, dos cayeron en la inconciencia, cinco mostraron tetraplejía, siete paraplejía L-1. Se les suministró oxígeno hiperbárico en cámara de decompresión, y los tetraplégicos bajaron a un nivel torácico. En dos casos la paraplejía se quedó en el mismo nivel. Los otros tuvieron mejor evolución; la parálisis mejoró lentamente quedando con espasticidad e hipoestesia. Casi todos quedaron con impotencia sexual. El control de orina fue satisfactorio, solamente con gotereo ocasional. Esta relativa evolución benigna permitió que once de los trece volvieran al trabajo.

En general la incidencia de esta complicación del buceo es baja y el daño permanente al cordón por esta condición se cuenta de 2 - 4 por 1000 pacientes de una unidad de daño al cordón espinal.

(Sometido por José A. Arabia, MD)

CERVICAL SPINE INJURIES CAUSED BY DIVING INTO WATER

Jerzy Kiwerski - Paraplegia Vol 18 101-105, 1980

Artículo proveniente del Centro de Trauma al Cordon Espinal de Polonia relatando la experiencia con 194 pacientes que tuvieron trauma en las vértebras cervicales como resultado de lanzarse en zambullida a un cuerpo de agua llano desde 1965- 1978. En 182 casos el trauma final estuvo acompañado de daño al cordón espinal en la misma área. La mayoría de los pacientes (52 por ciento) demostraba signos de transección completa al cordón en admisión.

55 por ciento de los pacientes tratados mostraron mejoría. Los mejores resultados se obtuvieron en el grupo de pacientes más jóvenes, y según aumentaba la edad, la mejoría fue más pobre. El artículo continúa describiendo el tratamiento dado en cada caso dependiendo si el mecanismo del trauma fue en flexión, compresión o extensión del cuello. El estudio concluye que los tratamientos dados en cada caso fue el apropiado, ya que el 75 por ciento de los pacientes mostraban daño completo o substancial a la médula, y aún así hubo un 55 por ciento que mejoró. En la mayoría de los casos el tratamiento dado fue tracción craneal por 6 - 8 semanas seguido con estabilización por collar ortopédico.

(Sometido por José A. Arabía, MD)



What do you mean, you
lost a contact lens?

HEPATIC RADIOXENON ACCUMULATION IN AN ALCOHOLIC PATIENT

Jorge Martínez Díaz, BS, Julio V. Rivera, MD and
José M. Martínó, MD

Case Summary

A 25-year old male was seen in the Emergency Room on June 20, 1980 complaining of stabbing pain in the left hemithorax and dyspnea. Arterial blood gases revealed: pH - 7.44, pO_2 - 55.7 mm Hg, pCO_2 - 30.6 mm Hg, HCO_3^- - 20.4 mEq/L, total CO_2 - 21.5 mM/L. Electrocardiogram was within normal limits. The patient has history of smoking cigarettes daily, occasional cocaine inhalation, past heroin abuse, and history of heavy alcohol intake for several years. There is no history of diabetes mellitus. Hepatomegaly had been detected on past admissions. Review of past medical records revealed consistently elevated value for serum glutamic oxalacetic transaminase (SGOT) and elevations of lactic dehydrogenase (LDH) and total bilirubin.

Physical examination revealed a well-developed, obese male with blood pressure of 130/80 mm Hg. Lungs were clear. Hepatomegaly was not detected. SGOT arrived at 95 mu/ml. Serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase,

LDH, bilirubin and albumin were within normal limits. Pulmonary function tests were also within normal limits. A ventilation study with (^{133}Xe) did not show obstructive disease, but retention of the material in the liver was noticed during the "washout" phase (see fig. 1a and 1b). No liver biopsy was done.

After pulmonary consultation, the patient was discharged.

Comments

^{133}Xe is a "noble" gas, inert chemically, and is a fission product. It is used as a gas or in saline solution for lung perfusion and ventilation studies and for measuring cerebral blood flow. Radioactive gases are considered to be freely diffusible. Solubility is a more important factor than diffusion since diffusion equilibrium is rapidly achieved under normal conditions in all tissues. The inert gases are highly soluble in lipids. ^{133}Xe is the most lipophilic of the inert gases, except for ^{222}Rn . Bunsen solubility coefficient for ^{133}Xe in water at 20°C is 0.123 compared to 1.9 in lipid at 22°C.

The retention of ^{133}Xe in the liver in this patient was an incidental finding. The patient was asymptomatic, although he was

From the Nuclear Medicine and Psychiatry Services and the Veterans Administration Medical and Regional Office Center, and the Department of Radiological Sciences, University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

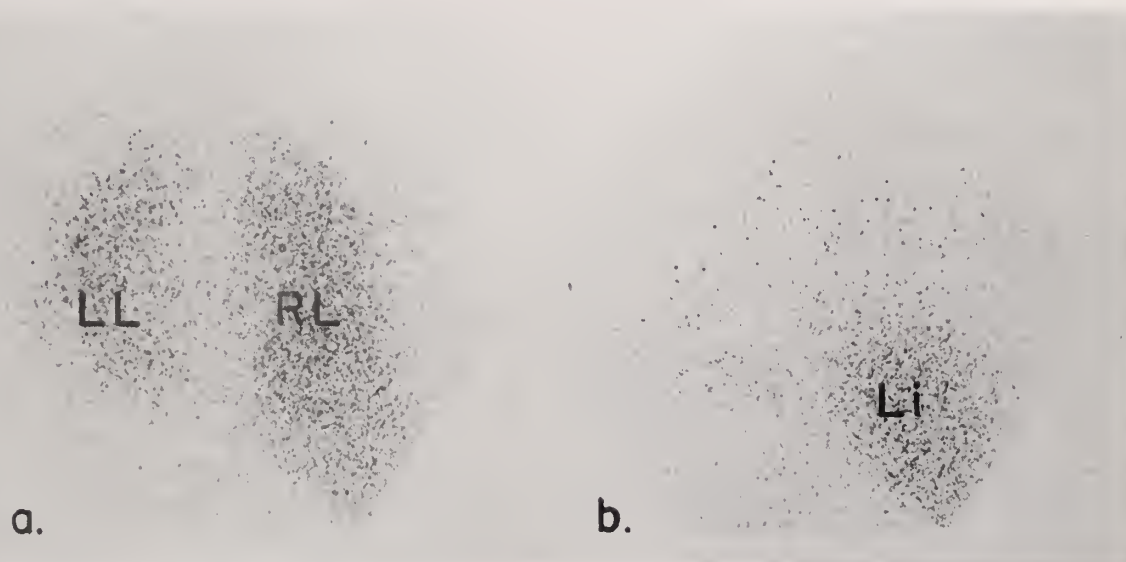


Fig. 1: Washout phase of ventilation study in the posterior projection. a. 0 -45 sec. b. 60 - 105 sec. Retention of radioactivity is noticed in the liver (Li) after it has cleared from the lungs (RL, LL).

obese, alcoholic, and presented persistently elevated values for SGOT. Liver biopsy represents the only certain method of establishing the diagnosis of fatty liver. This patient who has a history of psychiatric disease and was asymptomatic was judged to be an unsuitable candidate for liver biopsy.

Hepatic retention of radioxenon has been described in hepatic steatosis (1). Studies by Kitani and Winkler (2) have shown that the solubility of ^{133}Xe in human liver tissue *in vitro* correlates positively with the triglyceride content. No other condition which increases the accumulation of ^{133}Xe by the liver has been described. A correlation between ^{133}Xe studies and liver biopsies suggest that ^{133}Xe retention in the liver, provides a simple and specific test for fatty infiltration of the liver (3). Thus, although liver biopsy is the only certain method of establishing the diag-

nosis of fatty liver, ^{133}Xe retention may prove helpful in assessing this condition.

References

1. Ahmed, M., Witzum, K.F., Fletcher, J. W., et al: Xenon-133 accumulation in hepatic steatosis. J Nucl Med 18: 881-885, 1977.
2. Kitani, K., Winkler, K.: In vitro determination of solubility of ^{133}Xe and ^{85}Kr in human liver tissue with varying triglyceride content. Scand J Clin Lab Invest 29: 173-176, 1972.
3. Ahmad, M., Perrillo, R. P., Sunwoo, Y. C., et al: Xenon-133 retention in hepatic steatosis-correlation with liver biopsy in 45 patients. J Nucl Med 20: 397-401, 1979.
4. Subramanian, G., Rhodes, B. A., Cooper, J. F., and Sodd, V. J., eds: Radiopharmaceuticals, The Society of Nuclear Medicine, Inc. New York, 1975, p. 299-300.
5. Tubis, T., and Tubis, W., eds: Radiopharmacy John Wiley & Sons, Inc. New York, 1976, p. 749-750, p. 437, p. 448.
6. Isselbacher, K. J., Adams, R. D., Braunwald, E., et al: Harrison's Principles of Internal Medicine, 9th edition. McGraw Hill, 1980, p. 1487.

C U R S O S

Cardiology and Angiology

12-14 February 1981. Sixth International Joint Conference on Stroke and Cerebral Circulation. Los Angeles, California. Information: Administrator, Postgraduate Programs, American Heart Association, 7320 Greenville Avenue, Dallas, TX 75231 (214-750-5441).

Endocrinology

5-8 November 1980. Fifty-Sixth Annual Meeting of The American Thyroid Association San Diego, California. Information: Lewis E. Braverman, MD, Secretary, American Thyroid Association, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01605.

General Internal Medicine

12-20 February 1981. Pan-American Conference on Fertility and Sterility. St. Maarten, Netherlands Antilles. Information: U.S. International Foundation for Studies in Reproduction, Inc., 112-44 69th Avenue, Forest Hills, NY 11375 (212-544-7599).

Hematology

3-7 July 1981. Fourteenth International Congress of the World Federation of Hemophilia. San José, Costa Rica. Information: Roberto Cordero, MD (General Secretariat), P. O. Box 5127, San José, Costa Rica.

March 16-18, 1981

A Critical Evaluation of Diagnostic and Therapeutic Decisions in Gastroenterology (Course 009). Graduate

Hospital and the University of Pennsylvania, Philadelphia, Pennsylvania.

Director: Julius J. Deren, MD, FACP; Co-Directors: Henry Tumen, MD, FACP, and Moreye Nussbaum, MD.

Minimum Registration: 100 - Maximum Registration: 250.

Tuition: ACP Member, FACP, Resident, or Research Fellow - \$200. Nonmember - \$265; ACP Associate - \$150

Oriented toward family practitioners, internists, surgeons, and gastroenterologists, this course will emphasize critical evaluation of the need for, value of, and effects on management of various diagnostic studies in gastroenterology; and risk versus benefits of different medical and surgical therapies in gastrointestinal disorders. Brief, formal presentations by panel members will be followed by informal discussions.

March 23-27, 1981

Intensive Care Medicine (Course 011). St. Vincent's Hospital and Medical Center of New York, New York, New York.

Director: Dennis M. Greenbaum, MD, FACP, Co-Directors: James T. Mazzara, MD, FACP; John A. Crocco, MD, FACP; and Godfrey C. Burns, MD.

Minimum Registration: 50 - Maximum Registration: 170.

Tuition: ACP Member, FACP., Resident, or

Research Fellow - \$280; Nonmember - \$370;
ACP Associate - \$210.

Designed for practicing internists rather than intensive care specialists, this course will cover basic principles of intensive care and the care of the critically ill. Sessions will consist of didactic lectures followed by open panels, and seminars of smaller groups in which the material discussed in the didactic sessions will be covered. Special lectures and equipment demonstrations will also be held. Students will become familiar with apparatus and techniques used in the intensive care unit and with the pathophysiology of the commonest disorders seen in the adult medical intensive care unit. There will be ample opportunity for detailed discussion. Case studies, abstracts, and pertinent reference material will be available for each registrant.

April 1-3, 1981

Update in Infectious Diseases (Course 012). The Medical College of Pennsylvania. To be held at the Fairmont Hotel, Philadelphia, Pennsylvania.

Director: Donald Kaye, MD, FACP; Co-Director: Matthew E. Levison, MD, FACP.

Minimum Registration: 75

Tuition: ACP Member, FACP, Resident, or Research Fellow - \$200; Nonmember - \$265; ACP Associate - \$150.

Intended as a review of infectious diseases for the internal medicine board examination, this course will cover prevention, diagnosis, and therapy of certain changing or unusual aspects of infectious diseases. Topics to be discussed in depth include phagocytic cells, cellular immunity, humoral immunity, mechanisms of bacterial virulence and resistance to antimicrobials, hospital epidemiology, newer antibiotics, venereal diseases, diarrhea, fever of unknown origin, parasitic infections, bacterial infections, prophylaxis of bac-

terial infections, viral hepatitis, fungal infections, and tuberculosis.

June 15-19, 1981

Advances in Internal Medicine - Selected Topics (Course 020). University of Alberta Division of Continuing Medical Education, University of Calgary Division of Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada. To be held at the Banff Centre, Banff, Alberta, Canada.

Director: Allan M. Edwards, MD, FACP, FRCP (C); Co-Directors: Clarence A. Guenter, MD, FACP, FRCP (C); J. H. Sprague, MD, FRCP (C), and B. J. Sproule, MD, FACP, FRCP (C).

Minimum Registration: 100 - Maximum Registration - 150.

Tuition: ACP Member, FACP, RCP Member, Resident, or Research Fellow - \$280; Nonmember - \$370, ACP Associate - \$210.

Designed for the clinician internist, this course will be directed toward recent advances in selected subspecialties of internal medicine, with the accent on diagnosis and therapeutic skills. A number of workshop panels will accompany and augment the "state of the art" lectures and broad plenary sessions. Audience participation will be encouraged by question-and-answer periods after each half-day session and in the workshop panels.

The Department of Radiology and the Office of Continuing Education in the Health Sciences of the University of California, San Diego School of Medicine are offering a course: GASTROINTESTINAL RADIOLOGY WITH SPECIAL EMPHASIS ON IMAGING AND INTERVENTIONAL TECHNIQUES in San Diego, California March 16-19, 1981. The purpose of this course is to review selected topics in gastrointestinal radiology, placing emphasis on CT scanning, ultrasound

and interventional techniques. Discussion and questions on controversial topics will be encouraged. This course is designed for radiologists, but gastroenterologists will also benefit.

The Program Director is Gary B. Davis, MD. The guest faculty include Patrick C. Freeney, MD, University of Washington; Henry I. Goldberg, MD, University of California, San Francisco; and William M. Thompson, MD, Duke University. The faculty of the University of California, San Diego include: John A. Amberg, MD, John R. Amberg, MD, Robert N. Berk, MD, Gary B. Davis, MD, Lawrence E. Goldberger, MD, Barbara B. Gosink, MD, Alan F. Hofmann, MD, George R. Leopold, MD, Leslie S. Munick, MD, Harvey Rosenkrantz, MD, F. William Scheible, MD, and Andrew T. Taylor, MD.

The fee for the course is \$300.00 and 23 hours of Category I of AMA credit will be given.

For information, please contact Mary J. Ryals, Radiology, P. O. Box 2305, La Jolla, CA 92038, (714) 459-9787.

1980-1981 SCHEDULE

Programs in Continuing Medical Education

December 7-10, 1980, Williamsburg, Virginia

Coronary, Hypertensive, Valvular and Myocardial Heart Diseases: The Multidisciplinary Approach - William C. Roberts, MD, FACC, director Program 499

December 12-14, 1980, New York, New York

Cardiovascular Disease: Achievements and Challenges - 1980 - Henry I. Russek, MD, FACC, director Program 500

January 12-16, 1981, Snowmass, Colorado

Twelfth Annual Cardiovascular Conference

at Snowmass - John H. K. Vogel, MD, FACC, director; Bruce C. Paton, MD, FACC, co-director Program 501

February 2-4, 1981, San Diego, California

Clinical Echocardiography-1981 - Pravin M. Shah, MD, FACC, director . . . Program 502

February 9-11, 1981, New Orleans, Louisiana

Calcium (Slow Channel) Inhibiting Drugs in Cardiovascular Therapy: Mechanism of Action and Application - Borys Surawicz, MD, FACC and Attilio Maseri, MD, FACC, co-directors Program 504

February 19-20, 1981, Boston, Massachusetts

Ventricular Arrhythmia and Sudden Cardiac Death - Thomas B. Graboys, MD, FACC and Bernard Lown, MD, FACC, co-directors Program 505

March 30- April 3, 1981 - Indianapolis, Indiana

Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach - Charles Fisch, MD, FACC and Douglas P. Zipes, MD, FACC, co-directors . . Program 506

June 17-19, 1981, Washington, D. C.

The Patient with Arrhythmia - A Clinical Approach - Ross D. Fletcher, MD, FACC and W. Proctor Harvey, MD, FACC, co-directors Program 517

June 30- July 3, 1981, Snowbird, Utah

Eighth Annual Symposium on Clinical Echocardiography: Current Applications and New Developments in Cardiac Ultrasound at Snowbird Ski and Summer Resort - Arthur D. Hagan, MD, FACC, director; Anthony N. DeMaria, MD, FACC - co-director; William F. Friedman, MD, FACC - co-director Program 518

N O T I C I A S

AMA NEWS:

NEW TREATMENT ERA SEEN FOR MENSTRUAL PAIN

CHICAGO — A new era of treatment is at hand for menstrual cramps, says a report in the Oct. 24/31 *Journal of the American Medical Association*.

New medications are highly effective in relieving the pain that often accompanies the menstrual period, says a report in the *Journal's Medical News Section*.

For decades, an accepted approach to menstrual pain (officially known as dysmenorrhea) has been minor tranquilizers, mild pain relievers, and an automatic diagnosis of "psychogenic" pain, the report says.

Psychological factors may be strong in some cases of menstrual pain, but in many there are bodily changes causing the cramps, changes that can be offset by medications.

Gynecologists (physicians specializing in women's ills) are taking menstrual pain very seriously these days. The pain is known to cause loss of many woman-hours from work and school.

Menstrual pain is a complex process in the body, but an important factor is a high bodily production of a substance known as prostaglandins during the period of menstruation. The new medications reduce the excess prostaglandins production, and thus relieve pains.

Prostaglandin inhibitors are effective for relieving pain of dysmenorrhea in 65 to 100 per cent of women patients, Dr. W. Y. Chan, Cornell University Medical College, New York City, said.

However, says Dr. Chan, the prostaglandins represent a "shotgun" approach to the problem, and more selective drugs are sought for use in the future.

One problem, the report declares, is to reach physicians with the message that new tools are avail-

able for relief of menstrual pain. One family physician who treats many dysmenorrheic patients told JAMA Medical News:

"So many of the women come to me after seeing other physicians who have told them, 'It's all in your head.'"

RADIATION TREATMENT PROLONGS SURVIVAL IN LUNG CANCER CASES

CHICAGO — Treatment of inoperable lung cancer by radiation can more than double the survival time for some individuals, says a report in the Oct. 24/31 *Journal of the American Medical Association*.

The incidence of lung cancer has tripled in the last generation. Predominately a disease of men, it accounts for 25 per cent of all deaths from cancer each year.

Nearly one-third of patients with lung cancer are inoperable, James D. Cox, MD, of the Medical College of Wisconsin, Milwaukee, points out. Many of these individuals are virtually without pain, but they are nevertheless dying from a lung cancer that has already spread too broadly to be removed by surgery.

There has been disagreement among experts as to whether radiation actually it of benefit to these individuals, Dr. Cox says.

In the Milwaukee studies 92 patients with inoperable lung cancer were evaluated. Of 54 who were treated by radiation, 22 per cent survived five years. None of the 38 patients with untreated lung cancer lived beyond 27 months, he says.

Eight patients in the treated group were alive and well 53 to 100 months after treatment.

The study shows that patients with inoperable lung cancer having few symptoms can live many years if the tumor is controlled by radiation, Dr. Cox declares.

PHYSICIANS TO STUDY GENETIC ENGINEERING AND BRAIN HORMONES AT AMA SCIENCE MEETING

CHICAGO — Postgraduate courses, lectures and update workshops will be featured at the American Medical Association Winter Scientific Meeting Jan. 24-26 in Atlanta (Atlanta Hilton Hotel).

Complete program for the meeting is published in the Oct. 24/31 Journal of the American Medical Association.

Genetic engineering and brain hormones will be among the special topics presented by distinguished lecturers for the assembly. A special program will be offered on the physicians's role in nuclear power and possible nuclear accidents.

The AMA's annual Conference on Sports Medicine will be held in conjunction with the scientific meeting on Jan. 24. The AMA Auxiliary will present special programs for physicians' spouses during the meeting.

La Mar McGinnis, MD, of Decatur, Ga., is program director for the meeting.

Physicians will participate in lecture sessions and study courses on a wide variety of medical topics at the convention, says Richard M. Bergland, MD, chairman of the AMA's Council on Continuing Physician Education.

Study areas will include update on infectious disease, problems facing the American family, gastrointestinal disease, heart disease, pulmonary disease, drug therapy, nuclear medicine, bowel disease, acute

diarrhea, cirrhosis of the liver, exercise testing in heart disease, coronary by-pass surgery, management of acute respiratory failure, bacterial infections and antibiotics, viral infections, chronic mental illness, behavior problems in children, asthma, emphysema, drug interactions and venereal disease.

John T. Potts, Jr., MD, professor of medicine and chief of the endocrine unit, Harvard Medical School and Massachusetts General Hospital, Boston, will present the distinguished lecture on "Does the Dawn of Genetic Engineering Herald a Golden Age in Medicine?"

With recent public reports that gene splicing is approaching the commercial stage in American laboratories, physicians foresee a wide range of useful products from the ability to transplant a gene from one organism to another. Dr. Potts will discuss possible applications of gene splicing and genetic engineering to the everyday practice of medicine.

Another research field with great hope for the medical future will be aired in a distinguished lecture by Gavril W. Pasternak, MD, PhD, neurologist at Cornell University Medical College and Memorial Sloan-Kettering Cancer Center, New York City.

"Endorphins and Beyond: The Future of Brain Hormones in Clinical Medicine," will be Dr. Pasternak's topic.

Further information on the convention is available from the Department of Scientific Assembly, AMA, 535 N. Dearborn St., Chicago, IL 60610.

CERVICAL COLLAR RECOMMENDED AS CURE FOR SNORING

CHICAGO — Have a snoring problem? Already tried everything and still can't stop? And the rest of the family is threatening to move out?

Try sleeping in a cervical collar.

In the Oct. 17 Journal of the American Medical Association, E. L. C. Broomes, MD, of East Chicago, Ind., recommends using the collar, the same kind that is used for treating a sprained neck.

It works, says Dr. Broomes.

The discordant notes of snoring are usually at the maximum when the sleeping perpetrator is lying on his back with head sagging on the chest, the doctor explains. This causes bending of the trachea and compression of the respiratory tube, obstructing in and out flow of air. This obstruction causes the harsh sounds we call snoring, says Dr. Broomes.

The cervical collar will keep the chin elevated and so prevent flexing of the trachea that causes compression and results in snoring, the Indian physician declares.

CORONARY DEATHS DURING EXERCISE OCCUR IN THOSE ALREADY IMPAIRED

CHICAGO — The tales of middle-aged men who died during strenuous exercise are frequent enough to offer many individuals an excuse for avoiding exercise altogether.

But those men who die on the tennis court or the jogging track almost invariably are individuals

who already had serious heart disease, says a report in the Oct. 17 Journal of the American Medical Association.

The Institute for Aerobics Research, an exercise center in Dallas, Texas, kept records for more than five years on almost three thousand adults in an effort to determine whether exercise causes heart attacks.

There were only two heart attacks during exercise and no deaths during the study, reports Larry W. Gibbons, MD. Both men survived and were again exercising regularly.

"It appears that middle-aged men who die suddenly or have cardiac events in association with exercise usually are individuals with severe coronary disease", Dr. Gibbons says.

The Dallas physician cites other studies which found that of 63 cases of sudden death associated with physical exercise, no instance was found in which death could be regarded as due to the effects of extreme exertion on a previously healthy heart.

It is the combination of exercise and disease together that carries the major risk. Exercise places an additional stress on an already susceptible heart.

The conclusion is that there is a small, but not negligible, acute risk of heart attack for adults participating in vigorous exercise. But factors such as heart disease, competition, regularity of exercise and smoking may modify the risk.

Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Many Couples Overcome Infertility

Fertility Enhanced

Couples of child-bearing age who want a child become understandably concerned and frustrated when a planned pregnancy fails to occur.

This is a not uncommon occurrence. Some 15 per cent of marriages are involuntarily childless and another 10 per cent of couples have fewer children than they desire.

Advances in the past forty years in knowledge of infertility and what to do about it has made it possible for more than 50 per cent of couples with infertility problems to achieve parenthood, the American Medical Association points out.

Both husband and wife should undergo a general medical examination by their family or personal physician. He may refer the couple to specialists in evaluating fertility, or may perform the studies himself. The husband may be studied first because his examination is less time consuming and less expensive. In about 30 per cent of cases of infertility, the husband is the significant factor. In another 20 per cent he plays a contributing role. There may be factors that interfere with sperm production, sperm passage

or sperm delivery. There may be glandular problems.

The wife's urogenital system also requires evaluation. The opening of the uterus may be obstructed by heavy mucus, or there may be mucus of abnormal chemical properties that kill sperm cells.

Many times treatment will correct the problem. Or the physician can place the husband's sperm cells past the point of obstruction.

There are many physical reasons that could be involved in infertility. A common problem, however, is lack of proper timing of intercourse. The most likely time for conception is at or near the time of ovulation, usually about 14 days prior to the beginning of the next menstrual cycle. The time of ovulation can be detected by a slight rise in body temperature. Correct timing is more likely to produce conception than is frequent intercourse.

An investigation for infertility may be time-consuming. In some cases, examination and counseling by a physician may be all that is needed. In others, when problems are more complex, the solution may take more time and expense. While success cannot be guaranteed, pregnancy does occur in more than half of the infertile couples who seek help.

Artificial insemination, in which sperm cells from a donor are placed within the opening of the uterus, may permit the women to become a mother.



March, 1980
Frank Chappell
Science News Editor
AMA

In G.I. therapy



Adjunctive
Librax[®]

Each capsule contains
5 mg chlordiazepoxide HCl
and 2.5 mg clidinium Br

antianxiety/antisecretory/antispasmodic

for adjunctive therapy of duodenal ulcer*
and irritable bowel syndrome*

Librax[®]

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma, prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Bromide.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librax. Chlordiazepoxide HCl: Roche's known addic-

tion-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially, increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression, suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug

and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated, avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment, blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, i.e., dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

ROCHE

Roche Products, Inc.
Manati, Puerto Rico 00701

Motrin[®] vs codeine...

ibuprofen



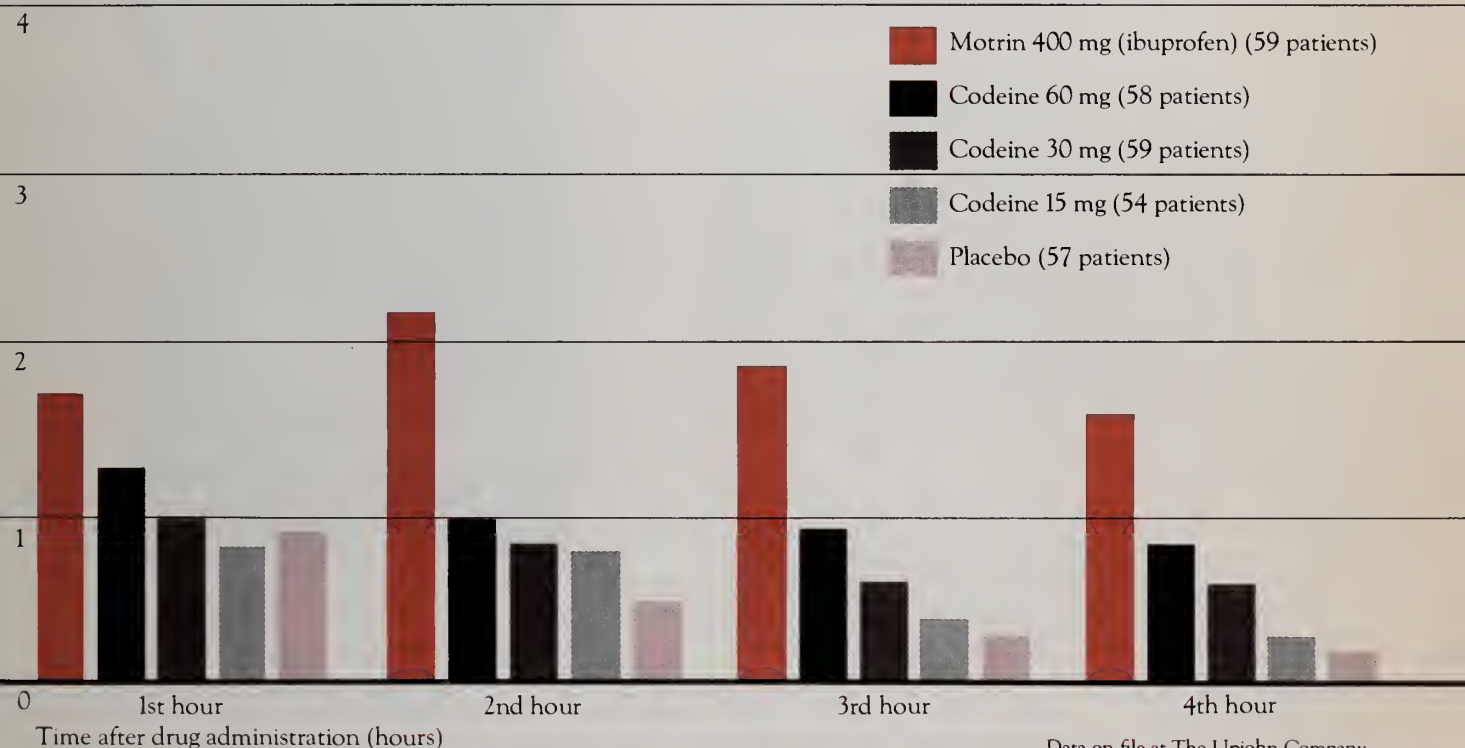
compare the analgesic effect

Motrin (ibuprofen) 400 mg tablets provided greater relief of pain than codeine in a double-blind, randomized clinical study of 287 patients.

Motrin was significantly more effective ($p < 0.01$) than codeine 60 mg at the 2-, 3- and 4-hour intervals...significantly more effective ($p < 0.01$) than codeine 30 mg, codeine 15 mg, and placebo at all intervals.

Degree of pain relief—mean scores

4 = Excellent relief 3 = Good relief 2 = Fair relief 1 = Poor relief 0 = No relief



One tablet q4-6h prn pain

A well-tolerated, nonnarcotic prescription for mild to moderate pain

Motrin[®] 400mg TABLETS
ibuprofen, Upjohn

- Not a narcotic • Not addictive • Not habit forming • Acts peripherally
- Relieves pain rapidly • Indicated in acute and chronic pain • Well tolerated
- The most common side effect with *Motrin* is mild gastrointestinal disturbance.

Please turn the page for a brief summary of prescribing information.

Upjohn

Her next attack of cystitis may require

the Bactrim[®] 3-system counterattack



ROCHE

Bactrim has shown high clinical effectiveness in recurrent cystitis as a result of its wide spectrum and distinctive antimicrobial action in the urinary, vaginal and lower intestinal tracts.

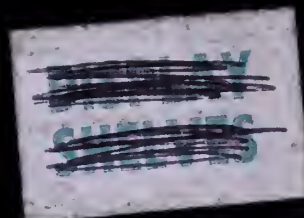
The probability of recurrent urinary tract infection appears to be enhanced by the establishment of large numbers of *E. coli* or other urinary pathogens on the vaginal introitus. The trimethoprim component of

Bactrim diffuses into vaginal fluid in effective concentrations, thus combating migration of pathogens into the urethra.

Studies have shown that Bactrim acts against *Enterobacteriaceae* in the bowel without the emergence of resistant organisms. Thus, Bactrim reduces the risk of introital colonization by fecal uropathogens. It has no significant effect on other normal, necessary intestinal flora.

Bactrim fights uropathogens in the urinary tract/vaginal tract/lower intestinal tract

Please see reverse side for summary of product information.



BOLETIN

ASOCIACION MEDICA DE PUERTORICO

CONTENIDO:

PACEMAKER SENSING MALFUNCTION

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VOL. 72

NUM. 12

DICIEMBRE 1980

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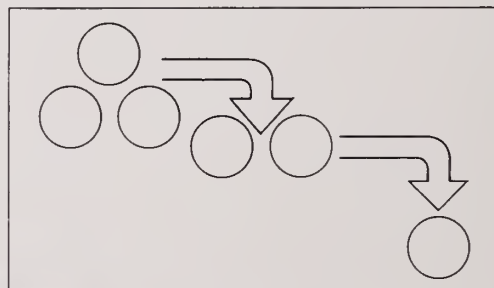
Elimination rates are gradual with Valium and thus provide a compatible adjustment interval for

the patient. In comparison, blood levels of short-acting agents with inactive metabolites decrease more rapidly and are more likely to be associated with withdrawal symptoms if medication is stopped abruptly.* With Valium unwanted effects other than drowsiness or ataxia are rare. Patients should be cautioned about driving and advised to avoid alcohol.

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*Sellers EM: *Drug Metab Rev* 8(1):5-11, 1978



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Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, atetosis, stiff-man syndrome, convulsive disorders (not for sole therapy)

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication, abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.

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Please turn page for brief summary of prescribing information.

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Description: TOLECTIN DS (tolmetin sodium) capsules contain tolmetin sodium as the dihydrate in an amount equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium.

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Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported.

If Tolmetin must be given to patients with active peptic ulcer, closely supervise the patients for signs of ulcer perforation or severe gastrointestinal bleeding.

Precautions: General—Clinical studies of up to two years duration have shown no changes in the eyes attributable to Tolmetin (tolmetin sodium) administration; however, because of ocular changes observed clinically with other non-steroidal anti-inflammatory drugs, ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.

There has been no evidence of renal toxicity to date in clinical studies; however, since Tolmetin is eliminated primarily by the kidneys, closely monitor patients with impaired renal function; they may require lower doses.

Tolmetin prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when Tolmetin is administered.

In patients receiving concomitant Tolmetin-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

Tolmetin should be used with caution in patients with compromised cardiac function.

The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g. sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips (e.g. Albustix®, Urstix®, etc.).

Usage in Pregnancy: Since Tolmetin has not been studied in pregnant women, the use of Tolmetin during pregnancy is not recommended.

Nursing Mothers: Because Tolmetin may be secreted in human milk, as a general rule nursing should not be undertaken while a patient is on this drug.

Drug Interactions: Although Tolmetin has been found *in vitro* to bind extensively to plasma protein, it does not alter the dosage of warfarin required to maintain a uniform prothrombin time.

In adult diabetic patients under treatment with either sulfonylureas or insulin, there is no change in the clinical effects of either Tolmetin or the hypoglycemic agents.

Adverse Reactions: Gastrointestinal System: The most frequent adverse reactions which occurred were gastrointestinal: nausea, 1 in 9 patients; dyspepsia, 1 in 10 patients; abdominal pain, 1 in 15; gastrointestinal distress, 1 in 15; flatulence, 1 in 25; diarrhea, 1 in 25; constipation, 1 in 40; vomiting, 1 in 30; gastritis, 1 in 55; and significant gastrointestinal bleeding without evidence of peptic ulceration, 1 in 240.

The incidence of peptic ulcer in about 3000 patients treated up to two years in clinical studies was about 1 in 50. Thirty-four percent of the ulcer patients had prior history of peptic ulcer disease and/or were receiving concomitant anti-inflammatory drugs, including corticosteroids, known to produce peptic ulceration.

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Body as a Whole: headache, about 1 in 10 patients; asthenia and chest pain, less frequently; and, rarely, anaphylactoid reactions.

Cardiovascular: edema, about 1 in 15 patients; hypertension, less frequently.

Central Nervous System/Psychiatric: dizziness or lightheadedness, about 1 in 20 patients; tension or nervousness, 1 in 50 patients; drowsiness, 1 in 60 patients; insomnia and depression, less frequently.

Dermatologic: rash, about 1 in 40 patients; pruritus, 1 in 60 patients; skin irritation, 1 in 55 patients.

Special Senses: tinnitus, about 1 in 65 patients.

Hematologic: Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred. This is similar to that reported with other non-steroidal anti-inflammatory drugs. A few cases of granulocytopenia have been observed.

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PACEMAKER SENSING MALFUNCTION

Charles D. Johnson, MD

Summary: This communication reviews and outlines complexities of pacemaker sensing malfunction, a slighted sphere of pacemaker technology and paraphernalia, veritably indispensable and meritorious for the clinical approach and management of the escalating multitude of pacemaker patients.

Resumen: Esta comunicación revisa y bosqueja las complejidades y el malfuncionamiento de la tecnología a los marcapasos y su parafernalia, necesaria, indispensable y meritoria por el acercamiento clínico, y el manejo de la escala múltiple de pacientes con marcapasos.

This is a review of sensing malfunction complexities pertinent to the neglected domain of ventricular-inhibited demand pacemakers. Demand (R-inhibited, VVI) pacemakers possess two independent functions which must be evaluated separately, namely, pacing the ventricles and sensing spontaneous or pacemaker-induced ventricular activity. Sensing failure, loss of demand function, can manifest as an

isolated defect but it is often associated with failure to capture (1-12).

Types of Sensing Failure

Improper sensing comprises:

A. *Oversensing:* by the physiological sensing of P and T waves, pacemaker "after potentials" (prolonged ventricular decay waveform), concealed ventricular extrasystoles (PVC's), myopotentials, environmental electromagnetic interference (EMI) (electrosurgical, diathermy, ignition systems, radar, microwave ovens, etc) and false or contact signals. Oversensing may manifest itself in various ways such as: pacemaker suppression or reversion to fixed rate mode (FRM), partial sensing, regular or irregular unexplained pauses without QRS complex or pacemaker spike (S), prolongation of the automatic interval (AI) or escape interval (EI) and slow or rapid pacing. A magnet eliminates all arrhythmias due to oversensing. Management consists of one or more of the following: avoidance, switching to the asynchronous mode, magnet application during surgical procedures and postoperatively, decreasing the sensitivity, reprogramming, changing from a unipolar to bipolar lead, antiarrhythmic drugs, overdrive pacing, relocating the generator site or enclosing the generator in a pouch. Modern electronic circuitry and shielding prevent much but not all of these far field signals. Excess sensing threshold range faci-

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litates interference (2, 4, 6, 11, 13-20).

B. *Undersensing*: which has an incidence < 1 percent to being relatively common, presents competition between the pacemaker and intrinsic QRS beats (FRM) and pacemaker parasystole. It results in palpitations, syncope, odd sensations, symptomatic hypotension (The Pacemaker Syndrome), a faster heart rate and the potential danger of R-on-T stimulation which rarely leads to ventricular tachycardia or fibrillation (Vf). This is possible during ischemia, acute myocardial infarction (MI), hypokalemia, augmented catecholamines and excess cardioactive drugs such as digitalis. A rate decrease usually transpires prior to loss of demand function (1, 4-5, 11, 13-14, 21-23). An insufficient signal reaches and alters the sensor which is blind, manifesting a S despite a QRS complex.

Undersensing is due to:

1) EMI (noise) satisfying certain voltage (V) and frequency criteria rendering the demand function temporarily inoperative from excess V range:

2) *Lead fracture* which may be partial, complete, intermittent, a loose connection or fracture of the *metallic coil*. This is recognized by a high V threshold, a low (< 1 mA), normal, high or erratic current (I) and a high fluctuating lead impedance (electrical resistance) > 1200 to 20000 ohms (normal lead system impedance = 250-1200 ohms; lead alone = 6-150 ohms). There may be a normal, slow or fixed rate, chaotic pauses (≤ 1 cycle), no capturing or sensing (when resistance rises sensing may fail before pacing), a small S, make and break false contact signals, oversensing, V signals of wide range amplitude, bursts of fast or isolated slow signals, a straight baseline with alternating current interference or no electro-

gram. An x-ray (PA, lateral, fluoroscopy, cinematography), magnet testing (S's are multiples of the AI), and perhaps suppression on chest wall stimulation (CWS) permit the diagnosis. An insulation tear only divulges a short circuit shunt of normal/low V, high I, low resistance (< 250 ohms), a bipolar electrogram of O, false signals and a change in the axis and amplitude of the S vector (The Leak Syndrome). Therapy is a new cable or unipolarization of bipolar leads (24-29).

3) *Generator Malfunction* - circuitry, battery exhaustion, decrease in input sensitivity (signal adequate) - is more likely in the older generator but can occur from fluid leakage between the terminals showing a normal V, I and impedance but failure of suppression on CWS up to 25 mA. A new battery or generator solves this. Pinto (30) reported a case of augmented circuit impedance with suppression on CWS secondary to fluid collection around the electrode at the proximal end (generator-lead connection).

4) *Malposition of Electrodes* with loss of sensor signal is the commonest cause of a sensing defect (2-20 percent of permanent endocardial electrodes; 5-20 percent or more of temporary electrodes). Malposition involves endocardial/epicardial electrode contact, ranging to a floating electrode or perforation of heart. It is diagnosed by an x-ray, changes in the threshold (high V and I, normal impedance), by S axis and amplitude, the electrogram, bundle branch block (BBB) pattern, a failure to capture, suppression on CWS and exclusion of a generator fault by radio signals. Careful electrode placement utilizing electrical testing and electrograms may help avoid malposition, while repositioning corrects it (1, 3-5, 30).

5) *Improper Slew Rate* ($< 0.3-0.5$ V/S) and *Voltage* ($< 2-3$ mV) of the cardiac signal is a true and common etiology of pacemaker sensing defects. It has been reported in electrode malposition, MI, relative electrical silence, cardiac fibrosis (normal S axis and amplitude), scarring and degenerative states, cardiomyopathy, pericardial fibrosis, a late electrode insulating sheath making poor contact proximity to viable myocardium and exit block. Also waveform distortion with abnormal splintered discoordinate signals, tall R waves rising in steps, segmentation of the intrinsic deflection (ID) misread by the pacemaker as a series of subthreshold signals, late deflection triggering, unstable signals such as PVC's, anomalous beats and exaggerated respiration, and delayed intraventricular conduction may fall under this category. The electrogram should be recorded during deep inspiration and coughing. The above problems may occur in severe heart disease, preterminal states, hypoxia, hyperkalemia, myxedema, antiarrhythmic drugs (quinidine, procainamide, lidocaine), pH, pCO_2 and electrolyte alterations.

While favoring oversensing, a unipolar system because of its greater interelectrode distance offers a larger antenna, a higher V for a given signal, usually a larger S and perhaps better sensing. Thus, pocket location can affect the signal size in unipolar installations. The signal can vary greatly and be quite small for an abdominal generator. Bipolar endocardial electrograms may present too small a signal for detection (2-16 percent) and less ST segment elevation than unipolar. Poor spatial orientation at 90 degrees of the signal depolarization pathway in respect to the two sensing electrodes with ID attenuation is a relatively common cause of < 2 mV signals (2, 23, 29, 31-36).

Selective sensitivity may or may not mean malfunction. A PVC may be sensed

while basic QRS complexes are not, or vice versa. Only selective PVCs (increased sensing impedance) may be sensed, as seen early after implantation when mechanical irritation tends to cause frequent PVCs with abnormal configuration resembling the paced beats (2, 7, 11, 19, 29, 35, 37-38).

These numerous slew rate disturbances may be diagnosed by x-ray, electrograms, high threshold capture, easy suppression on CWS, small R waves, high V (2 mV) and I (3 mA) and normal impedance. Management involves: a) turning-off the pacemaker and monitoring the patient if the underlying rhythm is adequate, b) reposition the patient, c) increasing the pacemaker rate to overdrive at 90-110/min and administering lidocaine for competing unsensed ventricular ectopy, d) unipolarization, e) repositioning of the electrode, f) replacement of the lead system and g) a high sensitivity, low threshold (0.8 mV) generator (1-5, 7-8, 11, 13-14, 19, 24, 27-28, 30, 37-41).

Delayed sensing, apparent malfunction, mimics sensing lack as the S falls within or near the end of the QRS complex producing a pseudofusion beat (PB). It is seen in the presence of sinus rhythm with BBB ipsilateral to the electrode, and with PVCs (wide) contralateral to the sensor electrode. It is relatively common and occurs with unipolar, bipolar, temporary and permanent units. Delayed arrival of the ventricular depolarization to the sensor due to the intraventricular conduction defect (IVCD) rather than a low dV/dt was believed to explain this. Sensing and recycling from different portions of the QRS complex in different beats causes slight differences in the intervals between S's. Sensing is normal on CWS (4, 11, 38, 42).

Fusion (FB) and Pseudofusion Beats - To avoid unnecessary generator or lead replacement, true sensing failure with the S falling

clearly outside and well beyond the QRS complex (at an interval after a spontaneous QRS which is shorter than the intrinsic EI of that particular pacemaker) must be distinguished from FBs and PBs. FBs are characterized by the pacemaker and a supraventricular or ventricular beat depolarizing different portions of the ventricles simultaneously producing variable QRS morphology; the natural QRS begins slightly before pacemaker inhibition would have occurred. PBs are characterized by the S falling upon and within a QRS of singular origin from 60-120 mS after onset of ventricular depolarization to which it does not contribute. It is fusion on paper of a pure spontaneous beat and an ineffective S. A large part of the surface ECG occurs before an adequate intracardiac signal has reached the sensor to suppress the S - an intracardiac to surface ECG asynchrony, and a reset delay of the sensing circuit. FBs and PBs are normal phenomena and occur when the spontaneous and pacing rates are similar and conduction delay exists between the depolarization and sensing sites. Differential diagnosis can be realized by long strips of ECG during deep respirations, changes of body position, slowing or speeding of the intrinsic rate from the automatic rate, magnet application and CWS (1-2, 7-8, 33, 38, 43-44).

6) *Other Sensing Determinants* - Other determinants of sensing are: a) generator/cable mismatch, b) sensing or source impedance (wire, tissue - 200-500 ohms including normal and fibrotic myocardial tissues, polarization - 2500 ohms or less) affected by R wave duration, the electrical metal (less with platinum-iridium) and size-contact area polarization (impedance increases for a smaller electrode), c) sensing circuit amplifier input impedance (5000-20000 or > ohms net) which should be matched against the electrode impedance; signal amplitude depends upon this ratio, the R being

progressively attenuated as the ratio decreases, d) leakage paths, e) the frequency response of bandpass filters, as 20-50 HZ frequencies usually require the least amplitude for detection (11, 26, 28-29, 32, 34-36, 41, 45). A mesh porous tip lead (CPI) may aid sensing.

Refractory Periods (RP). Escape Intervals

In order to diagnose arrhythmias and avoid unnecessary pacemaker replacement the pacemaker RP and EI must be appreciated. The RP provides for a normal brief period of demand sensor and pacer unresponsiveness and absence of recycling to an adequate spontaneous or artificial signal. *The delivery RP* (after emission of a pacing pulse) is 200-400 mS, and the *sensing RP* (several hundred mS after a spontaneous or artificial beat is sensed) are not necessarily the same. A short sensing RP allows detection of 2 signals in quick succession while a long RP allows early beats to go undetected. R waves are detected in the alert period. During the RP the sensing amplifier is saturated and deactivated.

A *relative RP* of 110-240 mS follows the RP when the demand mechanism has not regained full sensitivity (perhaps signal time and not V dependent), producing *partial sensing* and recycling manifested by inappropriately shorter irregular EIs (shorter than normal sensing but longer than complete sensing failure). This is associated with electrode malposition, PVCs and marginal 1.5-5 mV signals, as well as with normal pacemakers. It is managed by repositioning or unipolarization.

Malfunction may present as deactivation (recycling) of the pacemaker by a spontaneous QRS or PVC occurring during its preset RP, or failure of deactivation in that the S follows spontaneous depolarization at a shorter interval than the preset RP. Rate

hysteresis (longer EI) and reversion to FRM with continuous tachycardia in the noise sampling period (which comprises the final one-third or the first 75-125 mS after the RP) must be excluded.

The EI is the interval in mS between the onset of a normally generated sensed cardiac or other signal and the subsequent pacemaker S, and is usually the same as the AI. Supraventricular spontaneous beats and PVCs or escape beats (EB) of variable configuration initiate different EIs. The EI is apparently longer and variable in IVCDs from delayed sensing and recycling by as much as 120 mS (late PB). Short EIs occur in a) spontaneous cardiac signals in the RP, b) partial recycling and c) apparent malfunction of the noise sampling period (1-2, 4, 8-9, 11, 15, 33, 38, 40, 42, 46-47).

Electrogram

Sensing is triggered by the cardiac electrogram slew rate and amplitude, particularly the slew rate which is the rate of development or change in V amplitude as a function of time (dV/dt , frequency) of its ID, the vertical straight line portion. This is observed on an isolated battery-operated electrocardiograph (V lead for unipolar, lead 1 for bipolar electrograms) or better on an oscilloscope. Distal and proximal unipolar and bipolar electrograms should be obtained for temporary and permanent pacing. A typical right ventricular (RV) endocardial R wave will have an acute slew rate of 3 V/S (formula) or 0.3-1.6 V/S (estimated amplitude/time duration), a V amplitude of 5-15 mV and ST segment displacement of 4 mV, while chronic values are about 1.5 V/S, 15 percent less amplitude and no ST displacement. Slew rates < 0.5 V/S may not be sensed as attenuation

is significant. Frequencies of 20-50 HZ and signals of 15-30 mS and 2-10 mV amplitude are attenuated the least and detected the best by passband filters (pulse amplitude/frequency or width sensing response curve).

Programmability of the RP and sensitivity of QRS detection are now available so that sensitivity to a poor electrogram can be augmented (2, 4, 6-7, 13, 26-28, 32, 34-36, 40-41, 48).

Entrance Block

An adequate signal is necessary also for myocardial electrodes but since the site of implant can usually be selected there is little likelihood of this being inadequate (49). Yet an "Entrance Block" is possible secondary to pericarditis, fluid, blood, edema, inflammation, abscess and fibrosis around the electrodes as well as electrode hydrolysis and poor contact from surgical technique. Even sensing may fail in temporary bipolar surgical units (50). Rubenfire et al (51) reported 2 patients with sensing failure in the early postoperative period due to transient pericarditis (with rubs) at the electrode-myocardial junction (Medtronic 5841). A myocardial biopsy in Case 1 was normal. Corticosteroids and potassium appeared to be helpful, the patient recovering. The problem cleared spontaneously in Case 2 over 3-14 days. The Postpericardiotomy Syndrome is observed to a varying extent in 30-40 percent of epicardial implantations (52).

Testing of Sensing Function

Sensing may be tested noninvasively by the ECG, ambulatory monitoring, oscilloscope, x-ray, fluoroscopy, a magnet and CWS as part of pacemaker troubleshooting, the

diagnosis of arrhythmias and malfunction. Studies of the generator, leads and electrograms should be performed in all temporary and permanent primary and reoperative implantations. The data should be recorded in the patient's record with the pacemaker specifications.

Noninvasive

Magnet application converts the generator reed switch (closure) from the AI to the magnetic asynchronous FRM overriding and disabling the sensor, thus eliminating all causes of sensing failure. If the patient is in a dominant paced rhythm resetting and delay of the pacemaker Ss after an intrinsic beat or exercise indicates proper sensing. Otherwise, the generator may be inhibited (or Overdrive Suppression realized) by: 1) magnet waving for < 1 minute over some models alters the reed switch producing V mimicking a QRS complex. Complications are: rarely damage to the reed switch from too much, rapid movement which suppresses pacing or locks the pacemaker in a FRM, or erratic firing from improper application; 2) positioning an external programmer over the generator and pressing the button rhythmically; and 3) CWS by an external fixed rate pacemaker set at a slightly faster rate via suction cup electrodes applied closely together over the apex of the heart (bipolar leads), or over the apex (electrode tip) and the generator (unipolar) while recording a standard lead ECG. These external electrical signals are too weak to affect the heart but are interpreted as originating from the heart by their voltage and frequency characteristics, and will usually inhibit normal sensing circuits, especially unipolar. S inhibition indicates proper sensing but does not prove that a QRS would be sensed, which would be proven if an EB following the above maneuvers were correctly sensed.

CWS allows RP measurement, visualization of the underlying rhythm for diagnosis of arrhythmias and MI, temporary suppression of the R-on-T phenomenon and Vf and the differential diagnosis of undersensing. A low inadequate signal is suggested if the external signals rather than the spontaneous QRSs are sensed, especially if the AI is not changed. It does not suppress an abnormal generator but does suppress poor signal delivery (MI, altered vectors and increased circuit impedance). Suppression by stimulation directly at the generator-lead junction suggests a defective connection with a sensing circuit leak and high sensing impedance. CWS is relatively safe and simple. A rare possibility is that the pacemaker will not resume pacing on removal of the external unit. A failing Medtronic pacer may be suppressed. So, one must protect against asystole or escape rhythms by application for only 2-3 sec in a hospital under monitoring (2, 4, 7, 11, 14, 28, 30, 32-33, 40-41, 53-62, 79).

Sensitivity of an external temporary unit may also be examined by setting the sensitivity dial to a full clockwise position with the rate below the intrinsic rate of the heart. The indicator flicks to the left on sensing. Then, slowly rotate the dial counterclockwise and note when sensing disappears, the dial stops moving to the left and Ss appear. Record as "o'clocks" of the dial (12 o'clock = 6-8 mV, 3 o'clock = 3-4 mV). A Pacing Sensor Analyzer (PSA) can measure the pulse amplitude, interval, width, sensing and R wave height (32).

Testing At Surgery

Electrical testing at surgery plays a critical role. The PSAs (Medtronic 5300, CPI

2200, Cordis 209A, Pacesetter Programmalth and Teletronics PMA 200 which determines lead impedance also) aid and simplify operative testing - confer with their instruction booklets (27, 63, 65). Primary and reimplantation testing includes the A. *Pulse generator* - 1) rate, 2) pulse width, 3) pulse amplitude (10 mA I at the standard 500 ohms lead load = 5 V output), 4) sensing inhibitory capability or demand function; and B. *Lead-1*) stimulation threshold or threshold amplitude to capture. The recommended acute values are < 1 V (0.5-0.6) - 2-4 x threshold, and < 1 mA (0.7) I shown in the digital display of the PSA. Chronic values are < 3.5 V and < 2.5 -3.5 mA; 2) the electrical resistance which is usually calculated from Ohm's Law: $R = E/I \times 1000$, where E = output pulse amplitude in volts and I = resultant current in mA. This represents the pacing and sensing impedance, sensing being the greater; and 3) sensing, the goal of which is a R wave of 5-10 mV - 2-3 x threshold. The PSA detects the heart signal and generates an electronic digital readout displayed in mV. Its sensitivity calibration should correspond to that of the implantable pacemaker. Common test signals are square wave, sine wave, 1/2 sine wave, trapezoid wave, ramp/exponential and continuous.

A cardiac electrogram should be obtained. It is recommended to realize an amplitude of 6-8 mV, a time duration of 15-30 mS, an ST dome elevation (injury potential) of 2 mV or more at a slew rate of at least 1.5 mV/mS. These are suggested in order to accommodate the expected 40 percent slew rate and 15 percent V ID amplitude attenuation and the augmentation of time duration and frequency spectra changes, which transpire acutely to chronically, from fibrous tissue encapsulation of the electrode separating it and the myocardium (6, 11, 27-29, 34-36, 48, 63-65).

Surgical Implantation

Modern approaches for myocardial electrode implantation comprise 1) left parasternal extrapleural mediastinotomy, 2) inferior extrapleural mediastinotomy - subxiphoid, transxiphoid, transxiphisternal and left subcostal (preferred) - providing access to the RV; and 3) left anterolateral transpleural minithoracotomy providing access to the left ventricle (LV). In recent years the myocardial approach has enjoyed less popularity (10-15 percent) but is regaining favor with the rise of inferior limited methods and Hunter's sutureless, screw-in myocardial electrodes. A site relatively free of epicardial fat, fibrosis and coronary vessels offers the optimum for electrode insertion. The lower anterior RV wall is usually chosen, or the diaphragmatic-apical surface. A myocardial testing electrode (MTE, Medtronic 6017A) or probe has proven useful for the ideal stimulation and sensing parameters (closely predicts permanent values) as this site cannot be selected visually. Disparate values are found in adjacent areas.

Although a RV implant is frequently chosen and found satisfactory by many surgeons (rapid, low threshold in some, minimal postoperative morbidity, well-tolerated in poor-risk elderly), surgical pacemaker authorities (27-29, 35, 66) state that the LV is superior and is the chamber of choice for myocardial implantation for several reasons. The inferior approaches (except for the subcostal which may permit LV exposure) provide limited exposure and do not completely avoid pulmonary complications. The anterior RV wall is thin, friable, fatty, is subject to perforate with infarction, hemorrhage, recurrent pericarditis with effusion, tamponade, constriction and arrhythmias. The RV carries a higher-unsuitable pacing and sensing threshold than does the LV.

The anterolateral LV has a thicker

wall (avoid anterior surface and thin apex). and produces a better electrogram. Since the electrogram that triggers the demand pacemaker is largely LV in origin, the further the electrode is from the LV the more likely the signal will prove inadequate, emphasizing the role of depolarization origin. Furman has treated 8 referred patients with sutureless electrodes in the RV diaphragmatic surface which had failed to pace or sense, or both, early after implantation. Others have had similar experiences (28, 35, 66-78).

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ESTRONGILOIDIASIS EN EL PACIENTE INMUNOCOMPROMETIDO

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Resumen: El significado de los parásitos en el mundo ha sido parcialmente olvidado dado el mejoramiento de las medidas higiénicas y el nivel socioeconómico de muchos países. El descubrimiento de nuevas drogas con mejor actividad antiparasítica ha contribuido a disminuir el parasitismo. No obstante, la morbilidad que acompaña a las diversas parasitosis en algunas partes del mundo sigue siendo sumamente importante. Es más significativo e inquietante el papel que juegan algunos parásitos en el paciente inmunocomprometido. En éste, tanto la morbilidad como la mortalidad son elevadísimas. Solo la pronta y eficaz acción del médico puede ser el factor decisivo en la supervivencia de estos pacientes.

Introducción

El promedio de vida hoy día en Puerto Rico se encuentra alrededor de los 70 años. Gracias a la ciencia médica, personas que anteriormente vivían tres o cuatro décadas pueden ahora vivir muchos años más. Individuos diabéticos, enfermos renales y de cáncer, entre otros, se benefician de estos logros. Sin embargo, el progreso trae consigo nuevos problemas y nuevos retos al médico de hoy. Esto lo vemos en el paciente de cáncer y leucemia donde la enfermedad lleva consigo la disminución en la capacidad del individuo para luchar contra las infecciones. Lo vemos también en aquellos pacientes que por su condición necesitan ser tratados con drogas que a fin de cuentas también disminuyen dicha capacidad. Bacterias, hongos, virus y parásitos (9), todos ellos pueden ser responsables de enfermedad en este tipo de paciente inmunocomprometido. A continuación presentamos un repaso de la literatura médica en relación al problema de la infección por un parásito, *Strongyloides stercoralis*, en el paciente inmunocomprometido.

El parásito

Strongyloidiasis es una infección del

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intestino delgado causada por un nemátodo llamado *Strongyloides stercoralis*. Este parásito es cosmopolita y está ampliamente distribuido en el Sureste Asiático, Africa, Suramérica, Norteamérica y los países del Caribe. El gusano adulto mide 50 micras de diámetro por 2 mm de largo y habita normalmente el terreno húmedo donde se aparea y deposita sus huevos. A partir de estos se origina una larva llamada rhabditiforme que muda y se transforma en otra larva, ésta con capacidad invasiva, larva filariforme. Es ésta la que penetra la piel humana, generalmente en los pies y alcanza la circulación sanguínea pulmonar. Atraviesa la membrana alveolo-capilar y cae en la luz del alveolo para luego ascender directamente hacia la tráquea siendo deglutida al llegar a la epiglotis. La larva completa su maduración a lo largo de este trayecto y ya en el intestino delgado la hembra fertilizada se incrusta en la mucosa siendo el macho eliminado en las heces. Contrario a otros helmintos, éste tiene la capacidad de reproducirse dentro del ser humano. Es la llamada *autoinfección*. Cuando las larvas nuevas están en la luz intestinal, estos pueden madurar y tornarse invasivas penetrando la mucosa e ir hacia el pulmón. Esta autoinfección se conoce como *endógena*. Pero eso no es todo, muchas larvas al ser expulsadas en las heces quedan retenidas en las márgenes del ano y son capaces también de penetrar la piel a ese nivel. Esto se conoce como *autoinfección exógena* (14). El fenómeno descrito es importante porque nos explica la enorme población del parásito aún 30-40 años después de la primera exposición del huésped al terreno. Explica también lo que conocemos como hiperinfección que veremos más adelante.

Manifestaciones Clínicas

La infección es más frecuente en los

lugares de nivel socio-económico bajo. No hay límite de edad (2, 12), sexo o raza. Las manifestaciones clínicas están directamente relacionadas a la migración habitual del parásito. Las repetidas entradas a través de la piel originan a veces erupciones maculopapulares pruriginosas. No es raro el episodio de broncoespasmo o de neumonía transitoria que a veces es recurrente y que puede acompañarse de hemóptisis y eosinofilia. La radiografía es inespecífica, pero usualmente revela unos infiltrados en moteado. Cuando el gusano adulto o la larva se encuentran en el intestino, el individuo puede no experimentar sintomatología alguna o ésta puede ser vaga. Puede haber dolorimiento descrito como quemazón, que aumenta al ingerir alimentos y que suele localizarse en epigastrio sin irradiaciones, anorexia, diarrea mucosada sin sangre, estreñimiento, náuseas, vómitos y pérdida de peso. Algunas personas se presentan con un cuadro de malabsorción (5, 12). Los hallazgos físicos son inespecíficos, dolor a la palpación del abdomen, mientras que los radiológicos sugieren imágenes de duodenitis (5). La típica autoinfección exógena corresponde como ya vimos a la penetración de la larva en el área perianal. Se ha descrito un cuadro clínico llamado *larva currens* (del latín ligero), donde la larva sigue un trayecto visible que avanza unos 10 cm por día, diferente a la migración de *Necator americanus* por ejemplo (14). Esto puede acompañarse de edema, eritema y erupción petequial.

Hiperinfección

Cuando los síntomas pulmonares y/o digestivos arriba mencionados se exacerbaban hasta el punto de poner en riesgo la vida del paciente decimos que hay hiperinfección. Algunos autores separan este concepto del de diseminación donde se ven afectados los órganos

no incluidos en el ciclo de vida normal del parásito (12). Lo que sí es importante es que ambos cuadros conllevan una masiva invasión por parte del parásito. Entre los factores que predisponen a este cuadro se describen factores mecánicos y factores bioquímicos. Uno de los factores mecánicos que predispone a la hiperinfección es la existencia de un ileo paralítico; la larva es retenida más tiempo dando oportunidad a que madure y pueda ser invasiva (8, 12). Debemos recordar que el parásito puede a su vez contribuir a la producción de ileo paralítico. En pacientes con concentraciones bajas de enzimas gástricas e hipocloridia el factor bioquímico de riesgo se manifiesta. Esta condición permite que las larvas puedan sobrevivir y desarrollarse en tramos altos del intestino resultando en hiperinfección (3). Es el paciente inmunocomprometido quien más está expuesto a sufrir hiperinfección y diseminación (4, 7, 8, 10, 12). La respuesta inmune de la persona hacia los helmintos es tanto humoral como celular (12). La presencia de altas concentraciones de anticuerpos reagínicos, notablemente Ig E junto con manifestaciones típicas de hipersensitividad inmediata tales como edema, urticaria, disnea, diarrea y eosinofilia sugieren claramente la participación del sistema inmune humoral en las parasitosis (8, 12). Sin embargo, los estudios hechos demuestran que las alteraciones en la inmunidad celular constituyen el común denominador de los pacientes que sufren hiperinfección por strongyloides. La lista de las condiciones asociadas al cuadro clínico es grande; se puede mencionar uremia, cáncer, lepra, malnutrición severa, linfoma Hodgkin y no Hodgkin, sarcoidosis, quemaduras, candidiasis mucocutánea crónica, etc. En todos ellos puede encontrarse la evidencia clásica de la inmunidad celular deprimida, esto es, negatividad de las pruebas cutáneas de hipersensitividad retardada, contajes de

linfocitos T subnormales y de la producción de linfoquinas como el factor inhibidor de la migración (8, 12, 16). Experimentos hechos en ratas donde se ha inducido alteración de la inmunidad celular, se ha constatado la incapacidad de expulsar helmintos. Esta capacidad se normaliza después de restaurar la inmunidad por medio de la transfusión de linfocitos.

Inmunosupresión Exógena

Además de la condición intrínseca del paciente, el tratamiento con corticoesteroides y drogas inmunosupresoras deprimen la inmunidad celular (9, 13, 14). Se sabe que dosis mayores de 0.3 mg/kg/día de corticoesteroides pueden promover la salida de los linfocitos T de la circulación trastornando su capacidad de llegar al foco de infección. El efecto linfo-lítico de los corticoesteroides se conoce en algunos animales, mas en el hombre los datos no están totalmente claros (16). Se conoce también que los corticoesteroides aceleran la maduración de las larvas de Strongyloides en el intestino y reducen la inflamación a nivel local eliminando otra barrera al avance del parásito (12).

Hiperinfección-Clínica y Patología

La invasión por Strongyloides en el paciente inmunocomprometido no respeta órgano alguno (6, 10, 11, 14). Los síntomas clásicos de dolor abdominal, diarreas, náuseas, etc. aumentan en intensidad y duración. Las diarreas, usualmente mucosadas, pueden tornarse sanguinolentas y a menudo hay deshidratación, fiebre alta, peritonitis y shock (8, 12). Los hallazgos de autopsia revelan una infestación masiva con edema, ulceración, fibrosis

y enterocolitis hemorrágica. El tejido linfático adyacente se ve afectado y es frecuente la invasión de órganos vecinos tales como el hígado, páncreas, etc.

La afectación del pulmón origina pulmonía severa, abscesos y puede abocar a un fallo respiratorio que usualmente es fatal (4, 11). El paciente elimina gran cantidad de larvas en el esputo. La autopsia revela inflamación extensa con infiltrados celulares de predominio eosinofílico, en un campo plagado de larvas y gusanos adultos que se ubican en alveolos, bronquios y tejido conectivo.

Anormalidades neurológicas, desde cambios mentales hasta estupor y coma pueden acompañar a la infestación sistémica (12). Se cree que la larva llega al sistema nervioso central a través de la sangre arterial o del tejido conectivo perivascular (7). Las larvas se han encontrado en el espacio subdural, la aracnoides y en el interior de los capilares originando micro-infartos y necrosis por obstrucción.

Durante la hiperinfección por este parásito la incidencia de bacteremias por bacilos gram-negativos es mayor. Estas bacteremias suelen ser recurrentes y muchas veces refractarias al tratamiento. Las bacterias llegan a la sangre adheridas o excretadas por el nemátodo durante su migración a partir del intestino, o simplemente aprovechando el orificio de penetración de la larva en la mucosa de este órgano. De igual forma el cuadro descrito puede complicarse con episodios de meningitis bacteriana recurrente (12).

Aunque estas son las manifestaciones clínicas más comunes de la diseminación del parásito en el paciente inmunocomprometido, cabe señalar que puede imitar cualquier otro cuadro clínico. Esto a veces distrae nuestra atención a la hora de hacer el diagnóstico. Es por ello que lo más importante a este respecto es el pensar en esta entidad cuando nos

viene un paciente inmunocomprometido con síntomas de cualquier índole. La presencia de eosinofilia es clave, pero puede estar ausente, quizás debido al uso de corticoesteroides o a infecciones piogénicas concomitantes.

Diagnóstico

La confirmación se basa en el aislamiento del parásito a partir del examen directo o el método de concentración de heces (1, 5). Cuando el examen coprológico no nos ayuda se puede recurrir al análisis del aspirado duodenal. En un estudio realizado se pudo hallar la larva en un 27 por ciento de 952 muestras de heces examinadas por método directo y por el de concentración. El 91 por ciento de los pacientes de la serie dio positivo en el análisis del aspirado duodenal, pero 6 por ciento siendo positivos en excreta fueron negativos en el aspirado duodenal (5). Por ello es recomendable usar ambos procedimientos diagnósticos. El examen de esputo, orina, líquido pleural y tejido linfático puede ser de ayuda en el diagnóstico (12). Pueden emplearse pruebas serológicas como la de hemaglutinación indirecta y la de fijación del complemento, cuya sensibilidad es de un 75 por ciento, pero que no están al alcance de muchos centros hospitalarios (15). Se recomienda que todo paciente que vaya a recibir un trasplante renal se le hagan estas pruebas antes del procedimiento (13). Todo paciente con bacteremias o meningitis por enterobacterias recurrentes o difíciles de erradicar debe hacernos sospechar esta condición.

Tratamiento

El medicamento de elección para el

tratamiento de strongyloidiasis es thiabendazole (Mintezol ®), que se administra a razón de 25 miligramos por kilogramo de peso dos veces al día por dos días. A veces se requiere un segundo curso de tratamiento. Es importante el estudiar y tratar a todos los miembros de la familia que estén infectados así como implementar medidas adecuadas de higiene cuando no las haya. Los efectos secundarios de este medicamento son numerosos: anorexia, náuseas, vómitos, elevación de las transaminasas hepáticas, leucopenia, neurotoxicidad e hipotensión. Algunos autores están interesados en el posible uso de mebendazole (Vermox ®) en el tratamiento de esta condición buscando evitar estos efectos secundarios. Hasta hoy los resultados obtenidos son controversiales (6).

Cuando se utiliza thiabendazole en un paciente anéfrico debe de medirse la concentración sérica del medicamento y de sus metabolitos o al menos nunca pasar de tres o cuatro días de tratamiento. Esta precaución debe tomarse ya que un 90 por ciento de la droga se elimina por el riñón en forma de metabolitos inactivos pero con potencial tóxico al acumularse en el paciente anéfrico (13).

El tratamiento de strongyloidiasis en un paciente inmunocomprometido debe ser sin dilación y enérgicamente. El paciente debe de seguirse de cerca utilizando análisis de heces diarios y aspiración duodenal a intervalos (7, 15). El tratamiento debe prolongarse de cinco a siete días o más si fuese necesario (12). En lo posible las drogas inmunosupresores y corticoesteroides deben discontinuarse o al menos reducirse durante el episodio. Se han reportado casos refracta-

rios al tratamiento donde ha sido necesario el uso de thiabendazole mensual (12).

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ROUTINE LABORATORY TESTS FOR ELECTIVE SURGERY IN PEDIATRIC PATIENTS: ARE THEY NECESSARY?

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Summary: A retrospective review of routine preoperative tests in 690 children was performed. There is a low yield of positive findings in the routine determination of prothrombin time (PT), partial thromboplastin time (PTT), and in the routine use of the chest x-ray as screening procedures in the elective pediatric surgical patient. Elimination of these tests from the preoperative battery of tests would reduce the cost by approximately 75 percent without altering the quality of medical care or patient outcome.

Resumen: Se llevó a cabo un estudio retrospectivo de las pruebas rutinarias preoperatorias en 690 pacientes pediátricos. Hay una tasa muy baja de pruebas positivas en la determinación rutinaria del tiempo de protrombina (PT), del tiempo parcial de tromboplastina (PTT) y en el uso rutinario de la radiografía del tórax en el paciente quirúrgico pediátrico electivo. La eliminación de estas pruebas como rutina, disminuiría el costo

del grupo de pruebas preoperatorias un 75 por ciento, sin afectar la calidad del servicio médico, ni el resultado operatorio.

In an effort to streamline operating procedures, many hospitals have adopted sets of standard or routine steps in dealing with certain defined clinical situations. Elective surgery in community hospitals is one such area where sets of standardized steps are completed in preparing the patient for surgical procedures. Among these is a battery of so called routine laboratory tests which are prescribed to all patients regardless of the diagnosis or/and proposed operation.

Certain considerations demand a re-evaluation of these policies. The increased awareness of the cost of medical care is spurring efforts to adequately identify the likelihood that the patient will benefit from a given procedure. In addition there are inherent dangers associated with some of the screening procedures, such as the radiation exposure in routine chest x-rays.

In order to determine the effectiveness of routine mandatory preoperative studies in the identification of potential problems in the elective pediatric surgical patient, we undertook the following study of screening tests at our hospital.

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TABLE I
Routine Preoperative Laboratory Tests: Pediatric Surgery

HEMATOCRIT

	<i>Number</i>	<i>Percent</i>
<i>I. Total Determinations</i>	689	100 percent
<i>II. HCT. > 35</i>	602	87.4 percent
<i>III. HCT. 30-35</i>	82	11.9 percent
<i>IV. HCT. < 30</i>	5	0.7 percent
<i>A) Surgery without change or complication</i>	4	80 percent *
<i>B) Surgery Delayed</i>	1	20 percent *

Methods and Materials

A retrospective review was carried out of the records of all children under the age of fourteen admitted for elective surgery to Hospital San Pablo during the period January 1, 1979 to December 31, 1979. These records were obtained by reviewing the listing of elective surgical cases in the Record Room Department, and by a cross examination with the official daily operating room schedule. A total of 690 patients fulfilled the criteria of age and admission for elective surgery. In all these patients the records were reviewed and the results of the hematocrit, white blood count, prothrombin time (PT), partial thromboplastin time (PTT), urinalysis (u/a) and the chest x-ray reports were tabulated. Analysis of these data forms the basis of this report.

Results

I. Population studied

There were 690 children under the age of fourteen admitted for elective surgery during this period. Forty one percent were females (285), and 59 percent males (405). The routine preoperative tests were performed in a high percentage of cases as follows: hematocrit in 689 (99.8 percent), white blood count in 686 (99.4 percent), PT in 626 (90.7 percent), PTT in 678 (98.2 percent), urinalysis in 688 (99.7 percent) and a chest x-ray in 682 (98.8 percent). The ages ranged from 1 month to 14 years with a mean of 5.1 years.

II. Individual laboratory tests

A. Hematocrit: (Table I)

A total of 689 children had hematocrit determinations preoperatively. Using the criteria of a hematocrit under 30 percent

TABLE II
Routine Preoperative Laboratory Tests: Pediatric Surgery

WHITE BLOOD COUNT

	<i>Number</i>	<i>Percent</i>
<i>I. Total Determinations</i>	686	100 percent
<i>II. W.B.C. < 4.5</i>	4	0.6 percent
<i>III. W.B.C. 4.5 - 11.0</i>	566	82.5 percent
<i>IV. W.B.C. > 11.0</i>	116	16.9 percent
<i>A) Surgery without change or complications</i>	107	92.3 percent *
<i>B) Surgery Cancelled or Delayed</i>	9	7.7 percent

(usual criteria used by the anesthesia section) we found a total of 5 cases below this level, for a 0.7 percent rate of abnormal results: 99.3 percent of the children had a hematocrit above 30 percent. There was a group of 82 children (11.9 percent) with hematocrits in the 30-35 range. The rest (87.4 percent) had hematocrits above 35. Of the 5 cases with hematocrit under 30 percent, four underwent surgery without a change in management or postoperative complications. The remaining case with the hematocrit of 29.9 percent had the operation delayed for 2 days, because of bronchial asthma. Therefore, in the 689 children whose hematocrits were obtained preoperatively only 5 had a level below 30 percent, and in each of these cases, it did not lead to change in the lead to change in the operative management or to postoperative complications.

B. White blood count: (Table II)

A total of 686 children had the white blood count determined. Using the laboratory criteria of 4.5 to 11.0 as normal, we found that a total of 566 (82.5 percent) of the white blood counts were normal. There were 4 cases (0.6 percent) under 4.5. There were 116 cases (16.9 percent) with a white blood count above 11. Again when we analyze those cases that fell beyond the levels of normality we find 9 cases (91.3 percent) whose management was altered by either delaying or cancelling the operation. The reason for cancellation or delay in these cases was one of several acute infectious processes, mostly upper respiratory infections, gastroenteritis and bronchopneumonia. In no case was the management altered when there was a high blood count without accompanying clinical

TABLE III
Routine Preoperative Laboratory Tests: Pediatric Surgery
PROTHROMBIN TIME

	Number	Percent
I. Total Determinations	626	100 percent
II.P. T. < 10	9	1.4 percent
III.P. T. 10-14	608	97.2 percent
IV.P. T. > 14	9	1.4 percent
A) Normal Compared to Controls	7	77.7 percent *
B) Repeated Normal	1	11.1 percent *
C) Surgery Cancelled, Delayed or Altered	0	0 percent *

signs or symptoms.

C. Prothrombine time (PT):
(Table III)

We took as normal a range of 10 to 14 seconds; 608 (97.2 percent) of the determinations fell within this range. There were 9 cases with a PT less than 10 (1.4 percent) and 9 cases with a PT above 14 (1.4 percent). Of the 9 cases with high PT, when compared to control values these results were normal in 7 cases. In one case the test was repeated and found to be normal. In another case with an abnormal PT of 17.8 (48 percent above control) the test was not repeated. In all these nine cases the planned operation

was carried out without change in management and without postoperative complications.

D. Partial thromboplastin time (PTT): (Table IV)

We took as a normal range 25 to 45 seconds. There were 653, or 96.3 percent of the test within this normal range. A total of 18 (2.6 percent) were below 25 and 7 (1 percent) were above 45 seconds. Of the seven test results in the high range three were repeated with subsequent normal results. Of the four not repeated, three underwent surgery without change in management or postoperative complications. There was one case with an abnormally high PTT which was cancelled,

TABLE IV

Routine Preoperative Laboratory Tests: Pediatric Surgery

PARTIAL THROMBOPLASTIN TIME

	Number	Percent
<i>I. Total Determinations</i>	678	100 percent
<i>II. P. T. T. < 25</i>	18	2.6 percent
<i>III. P. T. T. 25-40</i>	653	96.3 percent
<i>IV. P. T. T. > 40</i>	7	1.0 percent
<i>A) Repeated normal</i>	3	42.8 percent *
<i>B) Surgery not altered</i>	3	42.8 percent *
<i>C) Surgery cancelled</i>	1	14.2 percent *

TABLE V

Routine Preoperative Laboratory Tests: Pediatric Surgery

URINALYSIS

	Number	Percent
<i>I. Total Determinations</i>	688	100 percent
<i>II. Normal Urinalysis</i>	636	92.4 percent
<i>III. Abnormal Urinalysis</i>	52	7.6 percent
<i>A) Surgery without change or complication</i>	50	96.2 percent
<i>B) Surgery cancelled **</i>	2	3.8 percent * (0.3 percent)

TABLE VI
Routine Preoperative Laboratory Tests: Pediatric Surgery
CHEST X-RAY

	<i>Number</i>	<i>Percent</i>
<i>I. Total X-rays</i>	682	100 percent
<i>II. Normal X-rays</i>	662	97.1 percent
<i>III. Abnormal X-rays</i>	20	2.9 percent
<i>A) Surgery without change or complications</i>	18	90 percent *
<i>B) Change in Management</i>	2	10 percent * (0.3 percent)

but this was due to an upper respiratory infection. Therefore, there were no cases where an abnormal PTT led to an alteration in management (except for repeating the test).

E. Urinalysis: (Table V)

There were 688 urinalysis determinations in this group. Of these 636 (92.4 percent) were within normal limits. There were 52 cases (7.6 percent) that could be considered abnormal for one of several reasons: loaded with bacteria, 5; loaded with white blood cells, 3; more than 10 white blood cells, 36; and more than 10 red blood cells, 8. Of these abnormal urinalysis only 2 were repeated. One showed a persistent abnormality and the other was reported as normal. This large group of children with abnormalities reported in the urinalysis, underwent surgery without change in management or compli-

cations, except for 2 cases. One was cancelled for an upper respiratory infection and another for what became a documented urinary tract infection.

F. Chest X-Ray: (Table VI)

There were 682 routine preoperative chest x-rays taken. Of these, 662 or 97 percent were reported as normal. There were 20 (2.9 percent) read as abnormal. The reported abnormalities included 13 lung findings (increased pulmonary markings in 8; pulmonary infiltrate in two; granuloma in two; emphysematous bullae in one); skeletal abnormalities in six, and a cardiovascular abnormality in one. Of these 20 abnormal chest x-rays, there were no changes in management and no complications reported in 18 (90 percent). There was a change in management in 2 cases (10 percent) showing bronchopneumonia. Therefore, one

can report change in management in 2 of 682 chest x-rays, for an overall rate of 0.3 percent.

III. Cases cancelled, delayed, or with postoperative complications

We looked at the group of patients from the point of view of those that were cancelled, delayed or who developed postoperative complications. There were 35 such cases. Seventeen cases were cancelled. Of these 10 had completely normal laboratory results. The reasons for the cancellation were upper respiratory infection in 5, bronchitis or asthma in 3, acute gastroenteritis in 1, and fever in 1. Seven of these cancelled cases had 1 abnormal laboratory result. Of these three cases had an increased white blood count and the reason for cancellation was an upper respiratory infection. One had an increased PTT and the reason for cancellation was an upper respiratory infection. Another had an abnormal urinalysis but again the reason for cancellation was an upper respiratory infection. Two cases had abnormal chest x-rays, and the reasons for cancellation were an upper respiratory infection in one, and a bronchopneumonia in the other. As can be seen, the abnormal PTT and urinalysis had no connection with the reason for cancellation. Five of the cases had a supportive evidence provided by the laboratories for cancellation but the main indications were the clinical findings.

We found 8 cases that were delayed. Of these 3 had completely normal laboratory tests and were cancelled for upper respiratory infection in two, and asthma in one. Five had one abnormal test: four of these consisting of an increased white blood count. Of those with abnormal white counts, two were cancelled because of gastroenteritis, one because of asthma and one because of a respiratory infection. The remaining abnormal test was a low hema-

tocrit, but the reason for delaying the operation was asthma.

There were 10 postoperative complications reported. Three had postoperative bleeding: following tonsillectomy in two, and circumcision in one. All had normal laboratory results. Acute gastroenteritis developed in 2 cases: one had completely normal preoperative values, and the other had a slightly elevated white count. There was a reported postoperative anemia in one case as a result of blood loss during the operation. There were no preoperative abnormalities in the laboratory results. Four minor complications were fever, upper respiratory infection, bladder atony and urinary tract infection occurring in one case each. The preoperative test gave no predictive indication of the complications that developed.

IV. Costs

We calculated the expenses associated with performing these routine tests. Assuming that the listed price is charged, a total of \$9,687.34 was spent in blood counts. The PT determinations involved an expense of \$8,801.56; PTT - \$9,532.68; urinalysis \$6,233.28; and the chest x-rays \$20,460.00. The total charges associated with these routine laboratory tests in elective pediatric surgical patients amounted to \$64,714.66 for these 690 patients. This represents approximately \$80 per patient.

Discussion

There is good evidence that certain routine screening procedures are not indicated based on their low yield in affecting patient management and outcome. The use of the routine chest x-ray has been most extensively studied. Brill and coworkers have

shown that the chest film is not indicated as a screening procedure in healthy children. This group found a 6 percent incidence of reportable findings on x-rays done in 1,000 healthy children. All of these findings were minor and none required treatment (1). Sagel et al conducted a prospective study in over 10,000 patients in whom a routine screening chest x-ray was obtained because of admission to the hospital or as a prerequisite to elective surgery. In 521 patients under the age of 20, no case of a serious abnormality was demonstrated on the routine x-ray. They propose that "the results of this survey strongly suggest that there is little rationale for routine chest roentgenograms in patients under the age of 20 with a localized pathologic process not usually associated with chest disease, simply because these patients are scheduled for an operation with general anesthesia or are admitted to the hospital". (2) Farnsworth et al in a recent review of 350 pediatric cases at their institution reach similar conclusions (3). Another group has analyzed data to suggest that the preoperative chest x-ray is justified in children. However, if one analyses carefully the data on their 1,500 patients, although 7.5 percent presented some reportable abnormalities, only 0.7 percent of these findings led to cancellation of the proposed surgery, and 2.2 percent led to minor alterations in the anesthetic technique, such as use of a cardiac monitor (which are routinely used in many hospitals), suction of the respiratory tract, or increased observation time after anesthesia. Of these cases 0.8 percent required a consultation with no change in management. There were no cases where a reported chest x-ray finding altered the surgical technique or led to postoperative complications. We believe that this data reveals a very low yield of significant changes in management brought about by unsuspected chest x-ray findings. Our own data shows that over

97 percent of 682 routine preoperative chest x-rays were reported as normal. Of the 20 x-rays reported as abnormal there were no changes in management and no complications reported in 18. We found therefore that there was a change of management in two cases out of 682, for a rate of 0.3 percent. To obtain the identification of these two cases, a total of \$20,460 was spent.

In addition to the low yield and significant expense associated with the use of routine chest x-rays in the preoperative pediatric patient one must add to the equation the risk of radiation exposure. It is estimated that diagnostic x-rays constitute more than 50 percent of all the radiation exposure to the general population (5). A pediatric population is particularly sensitive to the effects of this exposure in terms of possible genetic alterations or the long term development of malignancy.

Rourke believes that the task of finding the real diagnostic value of laboratory and x-ray procedures rests on the physicians. "The planners and the economists may not feel sufficiently knowledgeable to challenge the volume of laboratory and x-ray procedures carried out; this is a task best left to the physicians (6)".

Similar controversy has involved the use of other laboratory screening procedures. Schemel recommended that multiple laboratory screening, including liver function tests be done routinely in patients admitted for elective surgery (7). He based his recommendation on a study that found elevated enzymes levels in elective surgical admissions with an incidence of 1 in 700, and an incidence of clinical jaundice of 1 in 2,540. The implications of running the test to find this very low yield were presented by Crider who calculated a total cost of \$175,260 to run the program over one year (8). This amounted to \$15,932 per positive screening test, and \$58,420 for each patient that became clinically jaundiced. The impli-

cations of this cost on a national basis are significant.

The use of such biochemical profile in children has been reported and shown to make a small contribution to the overall care of the patient. In particular there was no significant advantage offered children admitted for surgical procedures and expected to stay less than one week in the hospital (9).

Our own data confirm these findings. The prothrombin time was found to be elevated in 1.4 percent of the cases using the usual ranges of normal. Of these nine cases, seven were found to be normal when compared with control values. Of the remaining tests, one was repeated and found to be normal. The other patient was operated without repeating the test. In all cases the planned operation was carried out without a change in management and without postoperative complications. We found a similar relation when reviewing the PTT. There were no cases where abnormal PTT led to alterations in management except for repetition of the test. The estimated expenses of routinely carrying out these tests were \$8,801 for PT and \$9,532 for PTT. The hematocrit determinations showed a similar low rate of abnormal results (0.7 percent below normal). The white count and the urinalysis yielded the highest rate of abnormal findings, with 16.9 percent of the white counts found to be above 11.0, and 7.6 percent of the urinalysis being considered abnormal. These abnormal results were used in a confirmatory manner, together with the history and clinical findings in altering the management. On review of the cancelled cases we found that the main reasons given were based on clinical findings (upper respiratory infections or other acute infections). Most of those cancelled had completely normal laboratory results. The white count was used mostly as confirmatory evidence of an infectious process. A similar set of findings was seen in those cases

delayed for short periods of time. Of the postoperative complications recorded in the entire group, the preoperative tests gave no predictive indications.

Evaluation of preoperative tests in elective surgical patients is only one area pertaining to the evaluation of cost effectiveness. Others have shown a high percentage of unnecessary laboratory tests in the emergency room and in the out patient clinic (10). In addition there is some data to suggest that there is no correlation between the physician's use of laboratory testing and clinical productivity, outcomes of care or estimates of clinical competence (11).

On the basis of these results we believe that routine preoperative screening should be kept to a minimum and possibly include only the complete blood count and urinalysis. These tests showed the highest yield of abnormal results and can be used as confirmatory evidence in evaluating clinical signs and symptoms. There appears to be no solid evidence for the routine use of the prothrombin time, the partial thromboplastin time and the chest x-ray as routine screening procedures in elective pediatric surgical patients. This is not to suggest that in cases where the physician suspects some abnormality, for example as with a history of previous bleeding or easy bruisability; or in the evaluation of fever, cough or rhinorrhea that these tests should not be freely ordered. However, there is little rationale to obtain these tests routinely in the otherwise asymptomatic child. By eliminating these tests one can reduce the cost of the panel of routine preoperative tests by approximately 75 percent, without affecting significantly the outcome of medical care. This approach would be in agreement with the recent policy statement by the American College of Surgeons that "preoperative laboratory testing and admission batteries of tests should be tailored to the needs of the patient and not

administered routinely to every patient entering the hospital (12)".

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THE ROLE OF BACTERIAL SURFACE FACTORS IN THE PATHOGENESIS OF INFECTIVE ENDOCARDITIS

During September of 1980 the Interamerican Congress of Cardiology will be held in San Juan, Puerto Rico. Prominent cardiologists of the hemisphere will meet here looking at the recent advances on heart diseases. To the physicians of today, infective endocarditis is not only the fascinating disease it always has been, but a new disease, which in today's world is posing complex problems of prevention, pathogenesis, diagnosis and treatment. In the last five years there have been important advances in the role of cellular surface factors in the pathogenesis of bacterial endocarditis. Puerto Rico has played a leading role in the research of these new advances with the work of Dr. Carlos H. Ramírez Ronda and co-workers, we will try to present them in a concised form.

*Bacteria most frequently associated with endocarditis in humans are aerobic, gram-positive cocci, including viridans streptococci, enterococci, and staphylococci (8, 9). In spite of the increasing incidence of gram-negative bacillary bacteremia (10), gram-negative bacillary endocarditis has remained unusual except in drug addicts (11, 12) and in prosthetic valve infections (13). Factors that determine the risk of endocarditis following episodes of bacteremia with various bacterial strains are largely unknown. Nevertheless, recent experimental studies concerning the bacteriology of mucosal surfaces suggest that bacterial adherence is an important property determining colonization (1, 14, 16) either by commensal or by pathogenic bacteria. Based on the previously presented data, the ability of bacteria associated with bacterial endocarditis to adhere to valve leaflets may be one of the pathogenic factors in the development of endocarditis. Gould, Ramírez-Ronda, Holmes and Sanford (1), compared fourteen strains of aerobic gram-positive cocci and gram-negative bacilli for adherence *in vitro* to normal human or canine aortic valve leaflets. The adherence ratios, or the proportion of bacteria initially incubated with remnants of valve leaflets that remained attached to the tissue, were significantly higher for enterococci, viridans streptococci, coagulase positive and negative staphylococci and *Pseudomonas aeruginosa* than for the Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae* (1). The organisms that most frequently cause bacterial endocarditis were found to adhere best to heart valves *in vitro*, these findings are compatible with the hypothesis that the ability of a micro-organisms to adhere to valvular endothelium is an important pathogenic factor in bacterial endocarditis in humans.*

*Further studies were carried out with *Streptococcus mutans* (2) and *Streptococcus sanguis**

(2, 17). *Streptococcus mutans* form on their surface glucosyl-transferases when the organisms are grown in the presence of sucrose. These enzymes synthesize glucans which can promote adherence of bacteria to each other and to endothelial tissues (18, 19). Ramírez-Ronda demonstrated that the adherence of *Streptococcus mutans* to damaged canine aortic valve leaflets was enhanced four-fold when the organism was grown in media containing sucrose which allowed for the production of dextran (2). Loss of dextran production did not affect adherence ratios for normal valve leaflets. Similar findings were reported by Scheld and collaborators for *Streptococcus sanguis* (17). Over 50 percent of cases of endocarditis are caused by dextran producing oral streptococci; one of the most frequent isolates is *Streptococcus sanguis*. Adherence of glucan positive streptococci was increased in the presence of dextran and decreased either in the absence of dextran production or in the presence of dextranase. Ramírez-Ronda studied the effects of molecular weight of dextran on the adherence of *Streptococcus sanguis* to damaged heart valves demonstrating that adherence is dependant on dextrans of high molecular weight, including commercial dextran T-2000 and glucans from *S. sanguis* or *S. mutans*. The studies also demonstrated, that low molecular weight dextrans can interfere with this adherence (3). Why then, do non-dextran producing microorganisms like enterococci and staphylococci also have a high affinity for damaged valves? Dextran production is one of the factors and not the only factor in the adherence of gram-positive cocci to damaged heart valves.

Beachey and co-workers have demonstrated that Group A streptococci bind to epithelial cell membranes by means of the micro-organism's lipoteichoic acid. Pre-incubating epithelial cells with lipoteichoic acid or pre-incubating Group A streptococci with antibody to lipoteichoic acid inhibited the adherence between the organism and the epithelial cells (20, 21). With this in mind and in view that teichoic acids are an integral part of the cell wall of many gram-positive microorganisms, Ramírez Ronda and co-workers studied the effect of teichoic acid on adherence of staphylococci to damaged heart valves *in vitro* (4, 4A). These studies demonstrated that when damaged heart valve leaflets were pre-exposed to teichoic acid, the adherence of *Staphylococcus aureus* to damaged heart valves was markedly decreased. The same studies were done with dextran producing streptococci (*Streptococcus sanguis* and *Streptococcus mutans*) and with non-dextran producing *Streptococcus faecalis* and enterococci. When damaged heart valves leaflets were pre-incubated with teichoic acid the adherence of *Streptococci sanguis*, *Streptococcus mutans*, *Streptococcus faecalis* and enterococci was markedly decreased. This decrease in adherence was independent of the production of dextran by *Streptococcus sanguis* and *Streptococcus mutans* (5). With these studies, Ramírez-Ronda and co-workers have demonstrated the possible role of teichoic acid in the adherence of gram-positive organisms to damaged heart valves. The "battle" to understand the pathogenesis of infective endocarditis has reached the cellular molecular level. We have just scratched the surface of a complex interaction between damaged host endocardium, host injury repair factors (platelets-fibrinogen), surface properties of host bacteria, and perhaps immune factors. The ultimate goal is to prevent the interaction of circulating bacteria with a nidus of platelet and fibrin. Will specific antibody to teichoic acid prevent such occurrence?

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ROENTGENOGRAM AND ELECTROCARDIOGRAM OF THE MONTH

This 46-year-old slightly mentally retarded male demonstrated decreased hearing, flushed suffused facies and eyes, mild clubbing and cyanosis, giant "a" waves in the neck, right heart failure, cardiac clues, marked polycythemia (Hb 20 g, Hct 65 percent) and hyperuricemia (8.4 - > 12 mg/100 ml). He died suddenly at swimming.

QUESTIONS

1. What are the clinical diagnoses?
2. Study the PA and lateral roentgenograms (Figure 1 - A & B). What are the findings and possible etiologies?
3. Describe the electrocardiogram (ECG) and make interpretation (Figure 2).
4. What are your complete anatomical and clinical diagnoses?
5. What is the recommended therapy?



FIGURE 1A

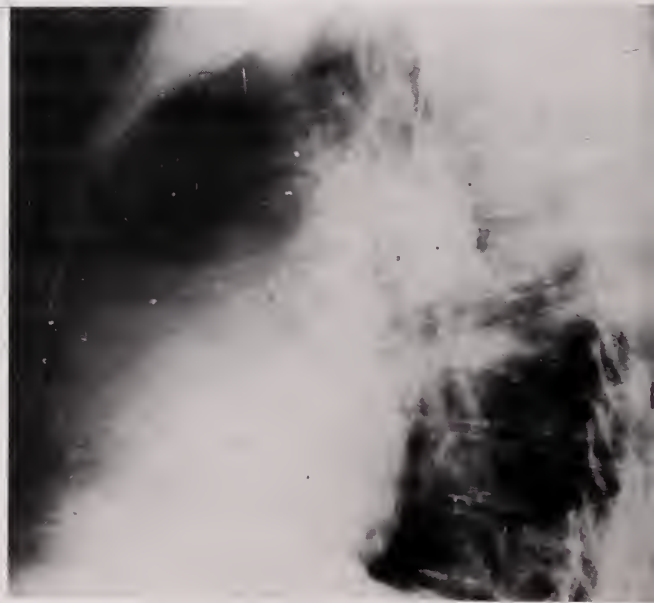


FIGURE 1B

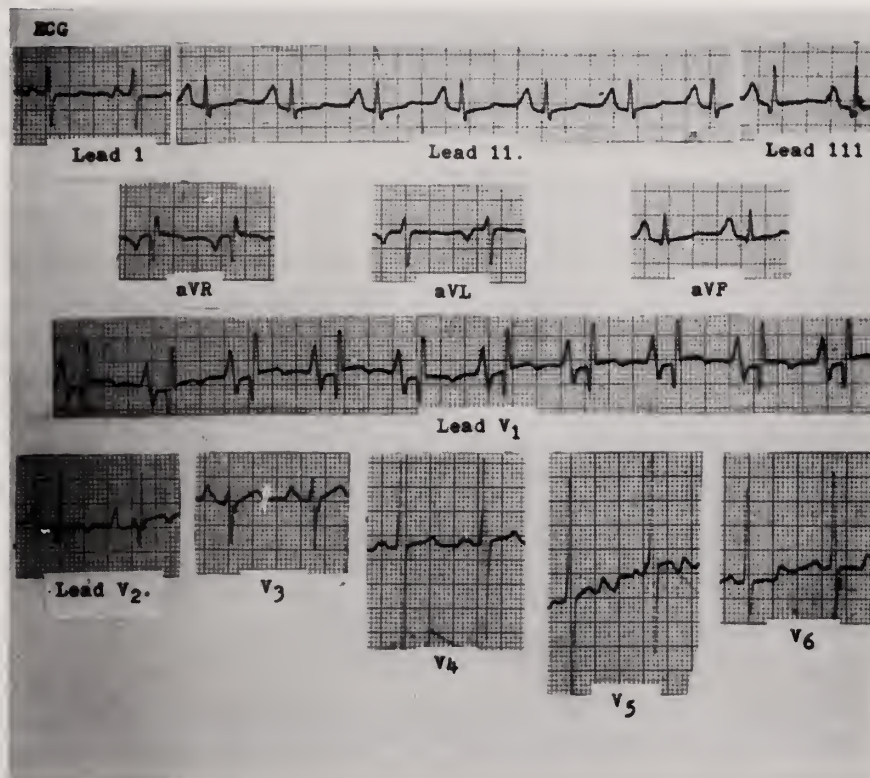


FIGURE 2

ANSWERS

Patent ductus arteriosus (PDA) with Eisenmenger's Reaction. Calcifications in pulmonary artery (PA), aortic knob and ductus arteriosus (DA). Surgery denied.

The roentgenograms are dramatic showing cardiomegaly with right ventricular enlargement (RVE) (rounded convex left heart border and apex, right ventricle occupies retrosternal space), probably some left ventricular enlargement (LVE), right atrial enlargement (RAE) (convex right heart), and huge main, right (24 mm diameter) and left PA's. Ring calcifications are present in the main PA (diam. er 32 mm) and aortic knob (30 mm), and calcifications are located between these in the DA, and probably right PA. These may have produced tracheal and left bronchial narrowing.

The ECG reveals: normal sinus rhythm, P axis = + 80 degrees, QRS axis + 110 degrees, P-R interval = 0.20 sec(S), QRS = 0.09-0.10 S. The P waves are —+ diphasic in lead 1, inverted in aVR and aVL, tall (3 1/4 mm) and broad (0.12-0.13 S) in leads 11, 111 and aVF, broad and notched in V_{3,4}, peaked (4 mm) in V₂ and huge +— diphasic in V₁. There are Q waves in lead 111 (no Q in leads 1, V_{5,6}), rSR' in V₁₋₂, QR in aVR, R/S complexes in leads 1, V₄₋₅ and Rs in V₆, with R waves of 25 mm in V₅ and 19 mm in V₆. T waves are low/diphasic in leads 1, 11, 111, aVL,

aVF, V₅₋₆, inverted in V₁₋₂ and upright in V₃₋₄. Diagnoses are: combined right and left atrial (LAE) enlargement, combined RVE and LVE (volume overload of right ventricle > pressure overload of left ventricle) and incomplete right bundle branch block (RBBB). The P-R interval is top normal.

DISCUSSION

Galen described the DA and its closure in 181 AD, and Giambattista Carcano in 1593. Victor Eisenmenger in 1897 described in a 32-yr-old male with a ventricular septal defect (VSD), hemoptysis, exercise intolerance, heart failure and cyanosis what is now known as Eisenmenger's complex - a large VSD with pulmonary hypertension (PH) and bidirectional or reversed shunt. PDA occurs in 1 of 200 live births or about 10 percent of congenital thoracic cardiovascular malformations, but is now rare in adults. PH is the result of a large PDA in infancy, and complicates a PDA uncommonly (5-17 percent with Eisenmenger's syndrome) (1-5).

ROENTGENOGRAPHY

The chest x-ray may be normal in PDA. With left-to-right (L → R) shunting cardiomegaly, LAE, LVE and enlargement of the ascending aorta and arch (knob prominent and pulsates) in adults are observed. The pulmonary trunk (PT) and its branches enlarge as increased pulmonary vascularity ensues. The cap of Zinn may be present. Infrequently the DA itself can be identified between the aorta and PT as a separate convexity. An aneurysm and diverticulum of the ductus has been reported (3, 5).

Associated with the development of PH (precapillary, high resistance vascularity) and Eisenmenger's syndrome, the volume overload of the left heart disappears so that the left atrium, ventricle and aorta assume normal size (or are so from the beginning). The heart size is normal, or at least prominent cardiomegaly does not exist. The right atrium and ventricle become mildly to moderately enlarged and dilated, but significant tricuspid regurgitation (congestive heart failure with sizable PDA and PH) can cause marked right heart enlargement. RVE forms an acute angle with the diaphragm and right atrial convexity is conspicuous. The PT and hilar vessels are quite prominent and dilated. The peripheral arteries are either normal or more likely to show a cut-off, tapering, attenuation or pruning appearance. The patent ductus can form an aneurysm or be dilated. Hearts with an initial L → R shunt tend to be larger than those with negligible or absent L → R shunt from infancy to early childhood; the left and right ventricles both enlarge, the PT and its main branches markedly dilate (3, 5-7).

ELECTROCARDIOGRAPHY

The ECG is influenced by pressure, flow and resistance relationships. It may be normal if the ductus is small. Not uncommonly, LAE with broad, bifid notched P waves occur in the standard, left precordial and V₁ leads with small or larger shunts. The P in V₁ may be diphasic with a deep

broad terminal force. LVE is common (66 percent) manifesting as volume overload- deep S waves in V_{1-2} , deep Q and tall R's, elevated ST segments and tall peaked T waves in leads V_{5-6} (or tall R in L 11, 111, aVF). ST depression may occur with marked LVE and can appear with upward concavity in L 11, 111, aVF, V_{5-6} (which is uncommon in other congenital heart disease). Large L \rightarrow R shunts with PH show biatrial and biventricular enlargement (large equiphasic R/S complexes in V_{1-6} , V_{2-4} , etc., Katz-Wachtel sign) in 10-34 percent. The QRS axis is inferior and leftward in the majority, with adolescence. Left anterior hemiblock (rare), RBBB or left BBB may be seen. Infants with the rubella syndrome may present an unusual superior, rightward or leftward orientation. The rhythm is usually sinus but atrial fibrillation (Af) in older cases with sizable shunts has been documented. Atrioventricular conduction time is prolonged in 10-20 percent of cases. Congenital complete heart block can exist in children and adults (3, 7-9).

The Eisenmenger ECG is characterized by right axis deviation (right inferior quadrant) and RAE (peaked narrow P's in L 11, 111, aVF, V_{1-2}). The P is often diphasic in V_1 with a peaked initial upright deflection and broad deep negative deflection; associated LAE shows broad notched P's in the standard and left precordial leads. RVE (tall monophasic R's with ST depression and inverted T's occur in the right precordial leads and deep S waves in V_6 , pressure overload) is characteristic. Severe RVE can show a qRs complex. There may be incomplete or complete RBBB with delayed superior, rightward and anterior vectors. Af or flutter can occur but arrhythmias are not frequent. No chamber enlargement is seen when both hypertrophied ventricles are balanced. Well-developed R waves without deep q or tall T's in V_{5-6} suggest a once existent L \rightarrow R shunt (3, 10).

CALCIFICATIONS

Calcification may be observed on frontal, lateral and oblique chest films, fluoroscopy, tomography and angiography. It can sometimes be identified in the ductal wall as a comma-like density between the PT and aortic knob. It may localize in the aortic arch and PA in long-standing PH and Eisenmenger's syndrome in older patients, especially women, and even in children and young adults. It was first described in PDA but since has been observed in atrial (ASD) and VSD's. Diffuse calcifications of the PA's extending into the lobar branches occurred in a 53-yr-old male with ASD, marked PH and bidirectional shunts (11). Calcium is present in the DA and adjoining aorta (not always visible by x-ray) in adults over 30 yrs of age and may make operative repair difficult and hazardous, requiring cardiopulmonary bypass or special techniques. In fact, a plaque near the caudal arch at junction of ductus is a valuable sign in young persons of a PDA, in whom atheromatous calcification of the aorta is otherwise rare. Calcification with PT enlargement and RVE often, but not always, indicate reversal of flow (3, 5, 6, 11-14). A 61-yr-old male who died suddenly, had a speck of calcium in the DA and arch, PA pressure of 50/22 mm Hg and complex arrhythmias (15).

Timpanelli et al (6) reported 4 women ages 34-65 yrs. with Eisenmenger PDA's, and calcifications on plain x-rays in or near the ductus (10-24 mm diameter), aortic knob, PA (11 cm diameter in one patient) and perivascular tissues. Autopsy revealed cardiomegaly, thrombi in PA branches, widespread sclerosis, atheromatous plaques and ulceration. The authors cited White & Bain's 85 and 66-year-old cases with extensive ductal and aortic calcifications, and others ages 25-52 years, while 3 cases ages 36-58 yrs had none. Calcified atheromas were found in a 4 1/2-yr-old female

with reversed PDA.

Pochaczewsky et al (14) reported 5 cases of PDA with combined arch and PA calcifications (3 in ductus too) ages 26-56 yrs. Two had RVE with $R \rightarrow L$ or bidirectional shunting. But 3 cases had LVE and $L \rightarrow R$ shunts; the PA's were prominent in 2 and 1 case had increased vascularity. It assumed a ringlike or curvilinear appearance in two. From their literature review covering the last 3 decades of either PA or aortic calcification in the young, none showed calcification in both sites except for PDA. Thus, combined localizations highly suggest a PDA with or without reversal of flow.

Calcium restricted to a PDA itself is unusual but has been seen in a large ductal aneurysm and not infrequently in obliterated ducti in childhood. Currarine (13) reported 75 cases of limited ligamentum calcification seen on x-ray as a dot or streak and at postmortem in infants and children where it may assume diagnostic significance. None had a PDA and such militates against patency of a ductus. It develops a few months to several years after normal ductal closure and probably disappears in many.

Main PA and hilar calcification is also observed rarely in long-standing PH of obstructive pulmonary disease, emphysema, PA aneurysms, chronic pulmonary emboli and thrombus, atheromatous disease, metastatic tumor, stenotic pulmonic valve, chronic pulmonary schistosomiasis and sarcoidosis (11, 14).

Aortic arch calcification is infrequent in isolated PDA in young females. But it occurs in the young with traumatic aneurysm of thoracic aorta, aortic coarctation, syphilitic aortitis, atheromatous occlusive disease, Takayasu's disease and rheumatoid arthritis (14).

PROGNOSIS

The average age of death of nonoperated patients ranges from 24 to 39 years. Noteworthy, there have been several long term survivors such as the 90-yr-old male of White, the 85-yr-old active school mistress of Bain who never had cardiac failure but died of gastrointestinal bleeding, another octogenarian (Boe); 74 (Aiken), 72 (Hornsten), 60 (Tohgi) and 56-year-old patients; and 70 years in Young's series, 5 of 69 cases being > 50 years of age (3, 5, 8, 10, 15-18).

Eisenmenger patients are uncommon but adult survival (2d-4h decade) are encountered. Most patients do well throughout adolescence and early adult life but become increasingly symptomatic during their 30's. Sudden death occurs presumably from arrhythmias. PDA comprises 14-18 percent of these, ages 18-47 years. One died at age 23 at cardiac catheterization and another at 34 years at cardiac surgery. Strenuous activity appears to be a risk factor (2, 7, 10). Syncope is uncommon (only 2 of 57 Eisenmenger patients) (10). With effort the systemic vascular resistance falls, $R \rightarrow L$ shunting augments and central nervous system oxygenation suffers. Arrhythmias may also play a role. PDA patients with Eisenmenger's syndrome pursue a more malignant course (earlier onset and progression of pulmonary vascular disease) in early life than do those with ASD or VSD (7, 10, 19).

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AVISO DE INTERES

La Junta Editora, consciente de su responsabilidad de hacer que el "Boletín" cumpla a cabalidad con su cometido de divulgar conocimientos médicos, elevar las normas de educación médica y al propio tiempo de llenar las necesidades de todos los compañeros médicos, ha acordado establecer una nueva Sección que se conocerá como "Sección de Preguntas".

Bajo esta nueva Sección, todos los compañeros tendrán la oportunidad de enviarnos preguntas médicas de casos difíciles o casos clínicos para opinión experta. Estas preguntas, con sus respuestas, serán publicadas en esta nueva Sección.

Las preguntas deberán ser enviadas a:

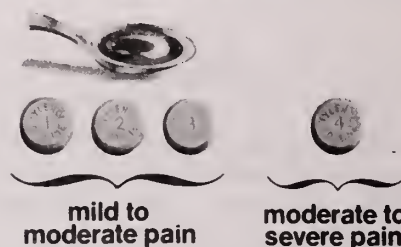
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Sección de Preguntas
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Santurce, P. R. 00908

Esperamos sus preguntas.

Juan M. Aranda, MD
Presidente
Junta Editora

TYLENOL[®] with Codeine

tablets  / elixir 



Summary of Prescribing Information

Description

Tablets: Contain codeine phosphate* No. 1—7.5 mg. ($\frac{1}{4}$ gr.); No. 2—15 mg. ($\frac{1}{2}$ gr.); No. 3—30 mg. ($\frac{1}{2}$ gr.); No. 4—60 mg. (1 gr.)—plus acetaminophen 300 mg.

Elixir: Each 5 ml. contains 12 mg. codeine phosphate* plus 120 mg. acetaminophen (alcohol 7%).

*Warning: May be habit forming.

Actions: Acetaminophen is an analgesic and antipyretic; codeine an analgesic and antitussive.

Contraindications: Hypersensitivity to acetaminophen or codeine.

Warnings: *Drug dependence:* Codeine can produce drug dependence of the morphine type and may be abused. Dependence and tolerance may develop upon repeated administration; prescribe and administer with same caution appropriate to other oral narcotics. Subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Caution patients that codeine may impair mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Interaction with other CNS depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) with this drug may exhibit additive CNS depression. When such a combination is contemplated, reduce the dose of one or both agents.

Usage in pregnancy: Safe use not established. Should not be used in pregnant women unless potential benefits outweigh possible hazards.

Pediatric use: Safe dosage of this combination has not been established in children below the age of three.

Precautions: *Head injury and increased intracranial pressure:* Respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: Codeine or other narcotics may obscure the diagnosis or clinical course of acute abdominal conditions.

Special risk patients: Administer with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Adverse Reactions: Most frequent: lightheadedness, dizziness, sedation, nausea and vomiting, more prominent in ambulatory than nonambulatory patients, some of these reactions may be alleviated if the patient lies down. Others: euphoria, dysphoria, constipation, drowsiness.

Dosage and Administration: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. TYLENOL with Codeine tablets are given orally. The usual adult dose is: Tablets No. 1, No. 2, and No. 3: One or two tablets every four hours as required. Tablets No. 4: One tablet every four hours as required. TYLENOL with Codeine elixir is given orally. The usual doses are **Children (3 to 6 years):** 1 teaspoonful (5 ml.) 3 or 4 times daily; **(7 to 12 years):** 2 teaspoonful (10 ml.) 3 or 4 times daily; **(under 3 years):** safe dosage has not been established. **Adults:** 1 tablespoonful (15 ml.) every 4 hours as needed.

Drug interactions: CNS depressant effect may be additive with that of other CNS depressants. See Warnings.

For information on symptoms/treatment of overdosage, see full prescribing information.

Full directions for use should be read before administering or prescribing.

TYLENOL with Codeine tablets are manufactured by McNeil Laboratories Co., Dorado, Puerto Rico 00646.

Caution: Federal law prohibits dispensing without prescription.

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McNeil Laboratories, McNEILAB, Inc.,
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In the Emergency Department

Potent pain relief without aspirin complications



TYLENOL[®] with Codeine

tablets  / elixir 

Tablets Contain acetaminophen 300 mg plus codeine phosphate* as follows:
No. 1—7.5 mg (1/8 gr); No. 2—15 mg (1/4 gr); No. 3—30 mg (1/2 gr); No. 4—60 mg (1 gr)
Elixir Each 5 ml contains 12 mg codeine phosphate* plus 120 mg acetaminophen (Alcohol 7%)

*Warning: May be habit forming

Please see facing page for summary of prescribing information

He's able to deal
with his fellow patients again.



Haldol[®]

(haloperidol)
tablets/concentrate/injection

Controls disturbed behavior in nursing home patients without undue sedation*

Highly effective for psychotic symptoms...

such as irrational behavior, confused thinking, agitation, hyperactivity, emotional withdrawal, hostility, suspiciousness. The ability of haloperidol [HALDOL[®]] to control troublesome symptomatology while preserving alertness and sociability would contribute significantly toward satisfying treatment goals and providing a better quality of daily life for the geriatric patient."

Smith GR et al. *Psychosomatics* 15:138, 3rd quarter, 1974

Minimizes likelihood of cardiovascular complications,** uncomfortable anticholinergic effects

"The lack of hypotensive effects ... suggests that haloperidol may be preferable to the phenothiazines in the treatment of mental disorders in the aged."

Tobin JM et al. *Geriatrics* 25(6):122, 1970.

"Among the antipsychotic drugs...haloperidol has the lowest anticholinergic potential."

Bernstein JG. *Clinical Psychopharmacology*
Littleton, MA, PSG Publishing Company, 1978, p 123

Especially useful for treating elderly patients with concomitant diseases

Unlike some of the other major tranquilizers, HALDOL haloperidol may be used concomitantly with other medications frequently prescribed for geriatric patients.

"There really are no drug interactions of major clinical importance involving haloperidol, which is a rather unique advantage of this drug."

Bernstein JG. *Management of Side Effects Related to Antipsychotic Drug Therapy* An Interview, 1978, p 12

* Although some instances of drowsiness have been reported, marked sedation is rare.

** Transient hypotension occurs rarely; severe orthostatic hypotension has not been reported.

Note: Extrapyramidal symptoms, when they occur, are readily controllable with antiparkinson drugs or dosage adjustment.

Please turn page for summary of prescribing information. Photograph posed by professional model.

injection

A rapid-acting injection for psychiatric emergencies: 5 mg haloperidol (as the lactate) with 1.8 mg methylparaben and 0.2 mg propylparaben per ml, and lactic acid for pH adjustment to 3.4 ± 0.2

concentrate

A tasteless, odorless, colorless Liquid Concentrate for better patient acceptability: 2 mg per ml haloperidol (as the lactate).

tablets

5 tablet strengths for convenience in individualizing dosage:

1 mg* 2 mg 5 mg*
1/2 mg 10 mg*

HALDOL® (haloperidol)
tablets/concentrate/injection

*contain FD&C Yellow No. 5 (see Precautions)

A dosage form for every therapeutic need

Summary of Prescribing Information

Contraindications: Severe, toxic CNS depression or comatose states from any cause, hypersensitivity to the drug, Parkinson's disease.

Warnings: Usage in Pregnancy: Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards. Infants should not be nursed during drug treatment.

Combined Use With Lithium: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity.

General: Bronchopneumonia, sometimes fatal, has followed use of major tranquilizers, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occurs, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL haloperidol may block its vasopressor activity and paradoxical further lowering of blood pressure may occur); (2) receiving anticonvulsant medication since HALDOL haloperidol may lower the convulsive threshold; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants. Concomitant antiparkinson medication, if required, may have to be continued after HALDOL haloperidol is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL haloperidol. When HALDOL haloperidol is used for mania in cyclic disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL haloperidol. FD&C Yellow No. 5 (tartrazine) may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Adverse Reactions: CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug

may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Persistent Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available haloperidol should be gradually withdrawn.

Persistent Tardive Dyskinesia: Although rarely reported with HALDOL haloperidol, tardive dyskinesia may appear during or after long-term therapy. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and sometimes appear irreversible; there is no known effective treatment and all antipsychotic agents should be discontinued. The syndrome may be masked by reinstitution of drug, increasing dosage, or switching to a different antipsychotic agent.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms.

Cardiovascular Effects: Tachycardia and hypotension. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication.

Liver Effects: Impaired liver function and/or jaundice reported.

Dermatologic Reactions: Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia and hypoglycemia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Autonomic Reactions: Dry mouth, blurred vision, urinary retention and diaphoresis. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration.

The injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

Caution: Federal law prohibits dispensing without prescription.

IMPORTANT: Full directions for use should be read before HALDOL haloperidol is administered or prescribed.

HALDOL tablets and concentrate (120 ml) are manufactured by McNeil Laboratories Co., Dorado, PR 00646.

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ABSTRACTOS DE LITERATURA MEDICA

QUIMIOTERAPIA CORTA EN PACIENTES TUBERCULOSOS CON ENFERMEDADES ASOCIADAS

William Stead et al, Little Rock Arkansas

Los autores presentan sus experiencias con 650 pacientes de tuberculosis pulmonar con bacteriología positiva tratados en los últimos cuatro años y medio con el curso corto de Isoniacida y Rifampín. El regimen consistía en usar:

1- RMP 600 mg.

2- INH 300 mg. diariamente por treinta días y luego RMP 600 mg., INH 900 mg. dos veces en semana por ocho meses.

El interés primordial de los autores era el encontrar si la eficacia del regimen sería afectada si el paciente tenía otras enfermedades o situaciones que sabemos que afectan el pronóstico o la morbilidad de la tuberculosis pulmonar.

En 110 pacientes las enfermedades asociadas eran:

1. Diabetes Mellitus - 45 pacientes

2. Malignidad tratada con radioterapia o quimioterapia - 32 pts.

3. Terapia de esteroides concurrente - 11 pts.

4. Gastrectomía previa - 11 ptes.

5. Retículos pulmonar coexistente - 10 ptes.

6. Silicosis avanzada - 1 pte.

La conversión a negativo de la bacteriología se retrasó solamente en el paciente con silicosis en el

cual la terapia falló. En el resto la conversión a negativo ocurrió antes de tres meses en el 80 por ciento de los pacientes y en el 100 por ciento de los casos, antes de los seis meses de terapia. Solo menos del 4 por ciento (3.6 por ciento) desarrolló Hepatotoxicidad cuando la medicación era diaria. Los restantes efectos secundarios fueron mínimos. El 62 por ciento de los casos se ha seguido por un período de 40 meses sin ninguna recaída.

Los autores, basándose en esta experiencia, concluyen que el curso corto de quimioterapia anti-tuberculosa no se ve afectado ni en su eficacia ni en su seguridad por la presencia de estas enfermedades o condiciones concomitantes a la tuberculosis pulmonar. La única enfermedad que parece requerir un tiempo de quimioterapia más prolongado es la silicosis para asegurarnos obtener la cura de la tuberculosis pulmonar concurrente.

(Sometido por Ramón E. Figueroa Lebrón, MD)

TOTAL HIP REPLACEMENT: ITS INFLUENCE ON SPONTANEOUS RECREATIONAL EXERCISE HABITS

Visuri T., Honkanen, R., Arch Phys Med Rehab Vol 61: 325-328, 1980.

El efecto del reemplazo total de la cadera en los hábitos de ejercicios recreativos se evaluaron en forma retrospectiva a través de entrevistas a pacientes operados en el Orthopedic Hospital de Helsinki, Finlandia. La edad promedio es de 63 - 68 años y su seguimiento de 2 - 4 años. La proporción

de pacientes que se involucraron en caminar regularmente aumentó de 2 a 55 por ciento, en ciclismo de 7 a 29 por ciento, en natación de 13 a 30 por ciento, en esquiar de 0 a 9 por ciento. El uso prolongado de la prótesis no tuvo efecto significativo en la intensidad del ejercicio. El ciclismo y la natación son formas de ejercicio especialmente valiosas después de reemplazo total de cadera puesto que la carga impuesta en la articulación por el peso se reduce.

(Sometido por Frank W. López, MD)

SPASTICITY: MEDICAL AND SURGICAL TREATMENT

Dimitrijevic Milan M - Neurology 30 (2): 19-27, July 1980

Registros electromiográficos de diferentes grupos musculares han sido obtenidos durante la evaluación sistemática de reflejos de acortamiento, reflejos cutáneos musculares, reflejos posturales y de activación volitiva. Esta data ha sido utilizada para proveer una base neurofisiológica en la selección de un tratamiento adecuado para la espasticidad. También nos ha servido dicha data para tener un conocimiento más profundo sobre la fisiopatología de la espasticidad.

En el tratamiento de esta condición se han empleado métodos farmacológicos que han resultado útiles como medida temporera únicamente. La hipertomía de un solo músculo puede ser tratada efectivamente con inyecciones de alcohol al 40 por ciento en la placa motora. Si se trata de una hipertomía en la cual está envuelto un grupo muscular, los autores recomiendan denervación parcial con solución de fenol en agua al 6 por ciento inyectada en el tronco nervioso. Espasticidad de varios grupos musculares puede ser tratada con rizotomía química o quirúrgica o miotomía. La hipertomía generalizada que envuelve los músculos del tronco y las extremidades puede ser modificada con el empleo de estimulación epidural crónica. También es posible conseguir modificar la actividad de músculos antagonistas recíprocos mediante

la estimulación eléctrica de los troncos nerviosos envueltos.

(Sometido por Rafael Aguayo, MD)

SEMIMEMBRANOUS INSERTION SYNDROME: A TREATABLE AND FREQUENT CAUSE OF PERSISTENT KNEE PAIN

Weiser, HI, Arch Phys Med Rehab Vol 60: 323-326 1979.

El síndrome de inserción del semimembranoso produce dolor en el aspecto medial de la rodilla. Este dolor se agrava con ejercicio, al bajar escaleras y flexión aguda de la rodilla. Se encuentra un área hinchada y elevada en la parte inferior de los "Hamstrings" mediales, rotación externa pasiva dolorosa de la rodilla y dolor a la palpación sobre el tendón de inserción del semimembranoso. 100 pacientes con este síndrome fueron tratados con inyección local de xilocaína y triamcinolona. Todos experimentaron alivio inmediato y temporero del dolor. En 58 pacientes el alivio fue de larga duración y 30 de ellos se le repitió el procedimiento en 3 - 5 meses. El dolor disminuyó y la incapacidad fue menos severa en 9 pacientes. En 18 pacientes el tratamiento falló y 15 pacientes no vinieron al seguimiento.

(Sometido por Jesús A. Maldonado, MD)

ORTHOSES FOR RHEUMATOID FINGERS

Koch Richard D, Bird David A, Orthotics and Prosthetics Vol 34: No. 2, 25-32, June 1980

Cuando tratamos artritis reumatoidea con deformidades de la mano se hace difícil conseguir una ortosis aceptable desde el punto de vista de la estética al tiempo que corregimos dicha condición.

En la deformidad de "Boutonniere" y "Swan Neck" que se consideran corregibles, la reducción del dolor y del edema se han conseguido tras la aplicación de un tipo de ortosis como las mencionadas. Tales ortosis deben ser livianas, no tóxicas, cosméticamente aceptables y ajustables sin que por ello se deformen o rompan. La ortosis de acero inoxidable además de reunir estas cualidades poseen un alto grado de durabilidad. Las ortosis de aluminio y plástico para corrección de "swan neck" resultan menos ajustables y más frágiles. El acero inoxidable resulta ser el mejor material en ortosis para el pulgar por las razones antes mencionadas.

(Sometido por Rafael Aguayo, MD)

THE USEFULNESS OF POWERED WHEEL-CHAIRS IN ADVANCED INFLAMMATORY POLYARTHRITIS

Bossingham, D. H. Russel, P., *Rheumatology and Rehabilitation* Vol 19: 131-135, 1980.

Artículo que expone la experiencia con 42 pacientes a los cuales se les prescribió silla de ruedas motorizada en el Mary Marlborough Lodge y en la Unidad de Rehabilitación de Oxford, England.

Concluye que pacientes con poliartritis inflamatoria avanzada (artritis reumatoidea, artritis reumatoidea juvenil, artritis psoriática y artropatía degenerativa) desarrollan tales deformidades óseas y debilidad muscular severa que una silla de ruedas motorizada se hace necesaria.

35 por ciento de los pacientes usaron una silla de ruedas motorizada sin alteraciones, pero 28 por ciento necesitaron alteraciones en el control de mando. Casi el 60 por ciento de los pacientes usaban su silla de ruedas motorizada diariamente; de esos 50 por ciento la usaban por más de ocho horas diarias.

Movilidad fue la razón principal para prescribir la silla y lo más importante para el paciente.

Otra enfermedad concomitante ocurrió en 21 por ciento de los pacientes y fue un factor que se consideró para la prescripción de la silla motorizada.

También se concluye que en pacientes que necesitan una silla de ruedas motorizada en su trabajo, deben tener dos sillas, una en el trabajo y otra en la casa.

(Sometido por José A. Arabía, MD)

UNA RE-EVALUACION EN LA LITERATURA DE: EL GASTO ENERGETICO EN LA MARCHA DEL NORMAL Y DEL IMPEDIDO

Steven V. Fischer, MD, Glenn Gullickson, Jr., MD, *Arch Phys Med Rehab* Vol 59: 124-133, March 1978.

Se re-evalúa la literatura concerniente a la marcha de personas normales e impedidas - amputados, hemipléjicos y parapléjicos. También se revisan los estudios hechos en el gasto energético de la marcha con aditamentos de asistencia y de silla de ruedas. De acuerdo con los resultados promedios que se encuentran en la literatura, una persona normal cambia aproximadamente 83 metros por minuto, con un gasto energético (E_e) de 0.063 Kcal/min/Kg y 0.00764 Kcal/metro/Kg. La persona impedida camina más despacio, para evitar un aumento del gasto energético por minuto (E_e /minute). A medida que la persona tenga más impedimentos, más pérdida de determinantes en la marcha se pierden; así caminará más despacio y será menos eficiente en términos de E_e /Kcal/ unidad de distancia. La importancia de una terminología en común cuando se mide el gasto energético en la marcha y la necesidad de permitir al individuo caminar a la velocidad más confortables son altamente recomendados.

(Sometido por Rafael Seín, MD)

EPIDEMIOLOGIA MOLECULAR DE INFECCIONES POR CITOMEGALOVIRUS EN MUJERES Y SUS INFANTES

Huang, E. S., Alford, C. A., Reynolds, D. W., et al - *New Engl J. Med* 303: 958-962, 1980.

Mujeres normales cuyo suero es positivo para anticuerpos en contra de citomegalovirus (CMV) frecuentemente liberan virus de uno o varios lugares incluyendo los tractos genitales y urinarios, la faringe y los senos. Esta excreción es episódica pero puede ser persistente, el CMV puede transmitirse en el útero y puede resultar en infección congénita a pesar de una inmunidad materna substancial, aunque el riesgo no se ha definido y aparenta ser bajo. Si la excreción viral es recurrente y la transmisión intrauterina en mujeres inmunes es causada por la reactivación de un virus latente, infección crónica de bajo grado, reinfección exógena o una combinación, no está resuelto.

Los autores estudiaron CMV de madres y sus niños para tratar de resolver el problema utilizando análisis de restricción de endonucleasas en ácido deoxyribonucleico viral purificado. Los autores encontraron que el CMV endógeno parece ser la fuente más frecuente de infecciones recurrentes y de transmisión intrauterina en mujeres inmunes.

(Sometido por Carlos H. Ramírez Ronda, MD)

UNA SÓLA DOSIS DE PENICILINA COMO PROFILAXIS EN CONTRA DE INFECCIONES NEONATALES CAUSADAS POR ESTREPTOCOCOS DEL GRUPO B

Siegel, J. D., McCracken, G. H., Jr., Threlkeld, N., Milvenan, B., and Rosenfeld, C. R. - *New Engl. J Med.* 303: 769-775, 1980.

Los estreptococos del grupo B han sido los

patógenos más frecuentemente recobrados de cultivos de neonatos enfermos en los Estados Unidos en la última década. La mortalidad es de 50 por ciento o más aún cuando se comienza tratamiento temprano. El enfoque ha sido la prevención. El uso de tratamiento profiláctico a la madre no ha sido efectivo. El uso de antibióticos a recién nacidos para profilaxis de oftalmía gonocócica en el Hospital Mount Sinai en Nueva York se ha asociado con la casi ausencia de infecciones por este microorganismo.

Los autores evaluaron en una forma controlada 18,738 recién nacidos entre 1977 y 1979. La tasa de colonización de las madres fue 26.6 por ciento con un 50 por ciento de concordancia en infantes no tratados y 12.2 por ciento en infantes tratados con penicilina G. La incidencia de enfermedad causada por los microorganismos susceptibles a penicilina en el grupo tratado con ésta bajó significativamente ($p=0.005$). Enfermedad causada por patógenos resistentes a penicilina aumentó en el grupo tratado con ésta durante el primer año del estudio más no durante el segundo. El uso rutinario de penicilina parenteral al nacer no es recomendada por los autores hasta que el efecto de ésta en la incidencia de enfermedad causada por patógenos resistentes sea definida.

(Sometido por Carlos H. Ramírez Ronda, MD)

CEFACLOR: UN GRUPO DE REACCIONES ADVERSAS

Murray, D. L., Singer, D. A., Singer, A. B. - *New Engl J Med.* 303:1003, 1980.

Cefaclor (Ceclor®), una cefalosporina oral con actividad en contra de *Hemophilus influenzae*, y efectiva para el manejo de otitis media en niños, ha tenido muy pocos efectos secundarios. En Lansing, Michigan, de noviembre 1979 a junio 1980, se encontró una erupción generalizada, con prurito y artritis de las rodillas y tobillos en ocho niños cuando se le estaba administrando cefaclor. Seis niños tenían sig-

nos de eritema multiforme y cuatro desarrollaron púrpura. Seis de los ocho niños recibían cefaclor por segunda vez. La erupción y/o artritis apareció de 5-19 días posiniciación de tratamiento y desapareció en 4-5 días después de discontinuado. La dosis que se administró fue 40-60 mg/kg/día.

Aunque esto es poco frecuente, y la dosis administrada fue alta, al prescribir cefaclor se debe de estar consciente de este efecto secundario raro y de ocurrir parar la administración del medicamento.

(Sometido por Carlos H. Ramírez Ronda, MD)

VACUNA CONTRA HEPATITIS B: DEMOSTRACION DE EFECTIVIDAD EN UN ESTUDIO CLINICO CONTROLADO EN UNA POBLACION DE ALTO RIESGO EN LOS ESTADOS UNIDOS

Szmunn, W., Stevens, C. e., Harley, E. J., et al: New Engl J. Med. 303:833-841, 1980.

Dienstag, J. L. (Editorial): New Engl. J. Med. 303: 874-876, 1980.

Se realizó un estudio doblemente ciego de 1,083 homosexuales a los cuales se le administró la vacuna de hepatitis B preparada por Merck, Sharp & Dohme Research Laboratories o un placebo.

La vacuna se encontró ser segura, con pocos efectos secundarios. A los 2 meses el 77 por ciento de los vacunados tenían niveles altos de anticuerpos en contra del antígeno B de superficie. Esto aumentó a 96 por ciento después de una dosis de refuerzo y permaneció así por la duración del estudio. Se desarrolló hepatitis B clínica o subclínica en 1.4-3.4 por ciento de los vacunados comparado con 18-27 por ciento de los no vacunados.

(Sometido por Carlos H. Ramírez Ronda, MD)

THE FROZEN SHOULDER: A REVIEW OF MANIPULATIVE TREATMENT

D. Thomas, R. A. Williams and D. S. Smith, Rheumatology and Rehabilitation, 1980, 19, 173-179

La patogénesis y el manejo del "frozen shoulder" sigue siendo controversial. Un repaso de la literatura sugiere que capsulitis constrictiva es un rasgo patológico común a casos crónicos y esto provee la racional para el tratamiento manipulativo.

Treinta pacientes con "frozen shoulder" fueron localizados al azar en dos grupos de tratamiento. Un grupo recibió manipulación e inyección local con esteroides y el resultado se comparó a otro grupo tratado con inyección local con esteroides solamente. Una evaluación al mes demostró muy poca diferencia entre un grupo y otro. A los tres meses el grupo tratado con manipulación e inyección de esteroides demostró gran mejoría en el arco de movimiento (40 por ciento), comparado al grupo que recibió la inyección solamente (13 por ciento). El grupo manipulado también demostró mejoría substancial en los niveles de dolor diario comparado a aquellos que solo recibieron la inyección (47 por ciento) y su incapacidad se resolvió en 47 por ciento comparado al grupo de solo la inyección donde únicamente el 13 por ciento no tuvo incapacidad.

El número de pacientes es muy pequeño en este estudio para que los resultados sean significativos estadísticamente, pero las tendencias que se demuestran son consistentes con otras series similares y sugiere que esta forma de tratamiento es lógica y efectiva.

(Sometido por Rafael Alvarez, MD)



New evidence is in: Treatment of mild hypertension can save lives

Even among patients with DBP in the low 90s, systematic therapy significantly reduced mortality:

- Of nearly 11,000 hypertensives identified by the Hypertension Detection and Follow-up Program, slightly more than 70% had mild hypertension (DBP 90-104 mm. Hg).¹
- Half were given systematic and aggressive care in HDFP centers; half were referred to customary sources of medical care.
- After 5 years, HDFP found that effective treatment of mild hypertension may reduce premature deaths by 20%.¹
- As part of HDFP's systematic treatment and follow-up program, the primary step-1 agent was chlorthalidone: Hygroton.^{®2}

**The primary agent used by the HDFP
in an effective low dose**

Hygroton[®] 25 mg.
(chlorthalidone USP)
one a day

**Because there's nothing mild
about mild hypertension**

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hypernatremia may occur or could be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and

related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aquea) in bottles of 100, 1000 and 5000; 25 mg. (peach) in bottles of 100 and 1000, unit-dose blister packs, boxes of 100 (10 x 10 strips).

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Septra[®] Suspension b.i.d.

Each teaspoonful (5 ml) contains: 40 mg trimethoprim and 200 mg sulfamethoxazole

a consistent performer in
treating acute otitis media
due to susceptible organisms.



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IN PEDIATRIC INFECTIONS

A powerful antibacterial performance

The efficacy of Septra has been substantiated in a study of 94 children with acute otitis media due to *H influenzae* and/or *S pneumoniae* (*D pneumoniae*). After 10 days' therapy with trimethoprim/sulfamethoxazole (TMP/SMX), the cure rate was 95.7%.^{1*}

A powerful performance against ampicillin-resistant *H influenzae*†

In another study of 16 children (aged 5–38 months) with purulent otitis media caused by *H influenzae*, it was noted that 10 days' therapy with ampicillin or amoxicillin produced no response in 14 patients. However, after 10 days' therapy with TMP/SMX, 93% of the 14 children responded favorably.² Additional *in vitro* studies have shown that when over 200 isolates of ampicillin-resistant *H influenzae* were tested, all proved susceptible to TMP/SMX.¹

A powerful “double-blockade” method of performing

Septra interferes with or hinders bacterial folate metabolism at two sequential points. This “double-blockade” action is believed to potentiate the effect of the component agents against sensitive bacteria.³

Please note, Septra is not recommended for the treatment of streptococcal pharyngitis. It is contraindicated during pregnancy and lactation, in patients hypersensitive to its components and infants under 2 months of age.

To date, there are limited data on the safety of repeated use of Septra in children under two years of age. Septra is not indicated for prophylactic or prolonged administration in otitis media at any age.

In vitro data do not necessarily correlate with clinical results.

*The criteria for success were (1) significant clinical response at 72 hours (2) all signs and symptoms normal at day 24.

†To date, clinical data on the effectiveness of Septra in the treatment of acute otitis media due to *H influenzae* with *in vitro* resistance to ampicillin and *in vitro* sensitivity to Septra are limited.

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EACH TEASPOONFUL (5 ML) CONTAINS: 40 MG
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A consistent performer in treating acute otitis media due to susceptible organisms.

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Each tablet contains: 160 mg trimethoprim and 800 mg sulfamethoxazole

Septa® DS Tablets Double Strength

Septa® Tablets

Septa® Suspension

INDICATIONS AND USAGE:

URINARY TRACT INFECTIONS: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

NOTE: Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of these urinary tract infections.

ACUTE OTITIS MEDIA: For the treatment of acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in the judgment of the physician Septa offers some advantage over the use of other antimicrobial agents. Limited clinical information is presently available on the effectiveness of treatment of otitis media with Septa when the infection is due to *Haemophilus influenzae* resistant to ampicillin. To date, there are limited data on the safety of repeated use of Septa in children under two years of age. Septa is not indicated for prophylactic or prolonged administration in otitis media at any age.

SHIGELLOSIS: For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

PNEUMOCYSTIS CARINII PNEUMONITIS: For the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period. Infants less than two months of age.

WARNINGS: SEPTA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS.

Clinical studies have documented that patients with Group A β -hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septa than do those patients treated with penicillin as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Deaths associated with administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides.

Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBCs are recommended; therapy should be discontinued if a significant reduction in the count of any formed blood element is noted.

PRECAUTIONS: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Since Septa may prolong prothrombin time in patients on warfarin, coagulation time should be reassessed when Septa is given.

ADVERSE REACTIONS: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septa. **Blood Dyscrasias:** Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. **Allergic Reactions:** Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic

myocarditis. **Gastrointestinal Reactions:** Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. **C.N.S. Reactions:** Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. **Miscellaneous Reactions:** Drug fever, chills and toxic nephrosis with oliguria and anuria. Periarthritis nodosa and L.E. phenomenon have occurred.

Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: The usual adult dosage for the treatment of urinary tract infections is two tablets or four teaspoonfuls (20 ml) every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage using Septa Tablets or Suspension.

Children: Two months of age or older:

Weight		Dose — every 12 hours	
lb	kg	Teaspoonfuls	Tablets
22	10	1 (5 ml)	1/2
44	20	2 (10 ml)	1
66	30	3 (15 ml)	1 1/2
88	40	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15–30	Half of the usual dosage regimen
Below 15	Use Not Recommended

PNEUMOCYSTIS CARINII PNEUMONITIS:

The recommended dosage for patients with documented *Pneumocystis carinii* pneumonitis is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. The following table is a guideline for the attainment of this dosage in children.

Weight		Dose — every 6 hours	
lb	kg	Teaspoonfuls	Tablets
18	8	1 (5 ml)	1/2
35	16	2 (10 ml)	1
53	24	3 (15 ml)	1 1/2
70	32	4 (20 ml)	2 (or 1 DS tablet)

HOW SUPPLIED: TABLETS, containing 80 mg trimethoprim and 400 mg sulfamethoxazole — bottles of 40, 100, 500 and 1000 tablets; unit dose pack of 100.

ORAL SUSPENSION, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored — bottle of 473 ml. Also available in double strength, oval-shaped, pink, scored tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole — Compliance™ Pak of 20, bottle of 60 and unit dose pack of 100.

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1. Data on file, Burroughs Wellcome Co.
2. Schwartz R, Rodriguez W, Ross S, et al: TMP-SMX in the treatment of otitis media secondary to ampicillin-resistant strains of *H. influenzae*. Second International Symposium on Recent Advances in Otitis Media with Effusion, Columbus, Ohio, 1979.
3. Kucers A, Bennett N Mck: *The Use of Antibiotics: A Comprehensive Review with Clinical Emphasis*, ed 3. Philadelphia, Lippincott, 1978, p 700.



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N O T I C I A S

AMA NEWS:

SILICONE BREAST IMPLANTS MAY EXPAND AT HIGH ALTITUDES

CHICAGO - What happens to the stewardess' silicone breast implants when the cabin pressure suddenly drops at a high altitude?

Do they blow up like balloons? Possibly even burst?

There is no ready answer. But there is a chance that the lady in question might be in trouble, says a report in the Nov. 14 Journal of the American Medical Association.

A stewardess who has had implants to enlarge both breasts asked this question of her doctor. If the plane in which she was working suddenly lost cabin pressure at 28,000 feet or higher, would she have discomfort, pain? Might the silicone envelope rupture?

Charles C. Fullett, M. D., of Atlanta, responded with some basic physics. Assuming the implants were done at sea level, at 18,000 feet the air in the implants would expand to twice original size. At 30,000 feet the expansion would be three times the sea level size.

It would be necessary to know the strength and elasticity of the silicone envelope to determine whether it would burst, Dr. Fullett points out.

"Although the skin overlying the augmentation (implant) is normally extremely elastic, one could assume that this anticipated degree of air expansion might create some discomfort at a minimum."

Dr. Fullett suggested that the stewardess could learn her tolerance by carefully controlled gradual exposure in a decompression chamber.

"Over the years," he says, "I saw many flight attendants with breast augmentation who had no com-

plaints from flying at normal airline cabin pressure, seldom above 7,000 feet."

ONE MILLION AMERICANS BITTEN BY DOGS EACH YEAR

CHICAGO - Dog bite has become an extremely common medical problem in the United States.

Each year at least one million persons are bitten by dogs, and the annual incidence is rising, says a report in the Nov. 21 Journal of the American Medical Association.

Dog bites now account for almost one per cent of all visits to hospital emergency departments, says Michael Callahan, MD, of the University of California School of Medicine, San Francisco. Dr. Callahan is in emergency medicine at hospitals in Oakland and Fresno.

Half of the dog bites are trivial, requiring little more than a swab of disinfectant. But at least 10 per cent of the bites require stitches and followup visits; one to two percent require hospitalization. Occasionally death results from attack by a dog or dogs.

A dog's teeth are not very sharp, but the jaw can exert a pressure heavy enough to penetrate sheet metal, Dr. Callahan declares. Thus, the result is a crushing injury with much damaged tissue, rather than a sharp cutting injury.

The average dog's mouth harbors at least 64 species of bacteria that can cause infection in humans, he says. Some two to five per cent of dog bite wounds seen in the emergency department become infected.

Deep wounds have a much higher infection rate, as do hand wounds.

Dr. Wise recommends that the doctor trim away crushed and torn tissue from the edges of the wound before sewing it up. Antibiotics to guard against infection might be in order, particularly in hand wounds or deep bites.

All of these wounds are exclusive of the danger of rabies, a serious illness requiring prompt and lengthy treatment to save the victim's life.

IMPOTENCE MAY BE SYMPTOM OF UNDISCOVERED DIABETES

CHICAGO — Sexual impotence might be a sign of a previously unrecognized diabetes in men, says a report in the Nov. 28 Journal of the American Medical Association.

Some 12 per cent of men troubled with sexual impotence were found to have previously undiagnosed diabetes in a study conducted at Queens Hospital Center, Jamaica, N. Y.

It had been known for some years that as many as 50 per cent of men with diabetes complained of impaired sexual function, Stanley Deutsch, PhD, of the School of Medicine, State University of New York at Stony Brook, points out.

Dr. Deutsch examined 58 men with sexual impotence and found that 12 per cent of them had cases of diabetes that had not been discovered by standard tests.

"When a man complains of impotence, diabetes must be considered as a possible cause," he declares.

STUDY CONFIRMS THAT MARIJUANA INGRE-

DIENT AIDS CANCER PATIENTS

CHICAGO — Further evidence that an active ingredient in marijuana is effective in relieving nausea in cancer patients who are taking strong drugs to control their disease is offered in the current Issue of an American Medical Association publication.

Leo E. Orr, MD, of the Southern California Cancer Center, Los Angeles, reports in the November Archives of Internal Medicine on a study of impact of tetrahydrocannabinol (THC), a principal ingredient of marijuana, in 55 cancer patients being treated with various combinations of potent drugs. THC is extracted from the raw marijuana and taken in capsule form, not smoked.

A serious problem in treating cancer with the potent anticancer medications is that the drugs themselves bring such severe nausea that it is difficult to continue their use in some patients.

Dr. Orr found that 40 of 55 patients receiving THC were free of nausea. Only eight of those 55 were free from nausea from another antiemetic drug, and only five of 55 were helped by placebos. The THC capsules worked better for some types of drugs than for others.

The users often obtained a "high" similar to smoking marijuana from the medication.

The THC capsules are not generally available to physicians, but still are considered experimental. The capsules used in the California study were obtained from the federal government's National Institute of Drug Abuse.

TECHNOLOGY ASSESSMENT FORUM ON CORONARY ARTERY BYPASS SURGERY: ECONOMIC, ETHICAL AND SOCIAL ISSUES

Sponsored by the National Center for Health Care Technology in collaboration with National Heart, Lung and Blood Institute, National Institutes of Health.

TO DISCUSS:

- Costs Incurred and Averted by Coronary Artery Bypass Surgery
- Organization and Use of Resources
- Ethical Considerations
- Quality of Life Issues
- Psychological Impact

WHEN: April 21-23, 1981.

WHERE: Sheraton Washington Hotel, 2660 Woodley Road at Connecticut Ave., N. W., Washington, D. C., 20008.

For technical information, please contact: Michael Eliastam, MD, Special Assistant to the Director, National Center for Health Care Technology, Parklawn Building, Room 17A-29, 5600 Fishers Lane, Rockville, MD 20857, (301) 443-4097.

For administrative information, please contact: Elaine M. Kokiko, Executive Vice President, Moshman Associates, Inc., 6400 Goldsboro Road, Washington, D. C. 20034, (301) 229-3000.

NEWS RELEASE FROM THE MEDICAL ECONOMICS COMPANY, A Division of Litton Industries, Inc./Oradell, N. J. 07649.

DRUG TOPICS magazine has reported that a new class of drugs offers dramatic promise to victims of coronary spasm, a condition once dismissed as a probably unimportant aspect of heart attacks but now recognized as a killer in its own right. Happily, a new class of drugs—calcium blockers or calcium antagonists—is being developed to control spasm.

Coronary spasm is not a newly discovered effect; it was postulated many years ago, but the equip-

ment for visualizing it didn't exist. A well-known failing of Western medicine is that it wants to deal only with what it can see, and researchers couldn't see spasm, except on rare occasions. Therefore most cardiac failure was attributed to atherosclerosis, which showed up frequently in autopsies. With the development of coronary angiography—the process of visualizing coronary arteries and branches—researchers began to see spasm fairly frequently.

The condition is caused by the entry of calcium into vascular smooth-muscle cells. Calcium apparently has several roles in coronary artery function, the DRUG TOPICS article points out, but just what they are isn't clear. It is known, however, the article continues, that the presence of calcium inside a cell triggers other happenings that ultimately result in contraction of the muscle. By shutting the gate on calcium, the new blocking drugs prevent this contraction or spasm.

Among the calcium-antagonists under study is nifedipine, from Pfizer Laboratory. Dr. Elliott Antman, clinical fellow at Peter Bent Brigham, Boston, delivered the research team's presentation, speaking for the 45 investigators who studied 127 patients with variant angina. The study results were quite dramatic: Anginal attacks were completely eliminated in 63 percent of patients; 87 percent of patients had a 50 percent or greater reduction in attack frequency. "The response rate was much too high to have been due to anything but the therapeutic efficacy of the drug," said Dr. Antman. When the therapy was intercepted, symptoms returned. "This strongly suggests that nifedipine is an extremely potent coronary spasmolytic," reported the doctor.

Verapamil, from Knoll Pharmaceuticals, another of the drugs under study, has been highly praised. A team in England called it "a very powerful antianginal agency with many desirable properties; it may be considered among the first-line drugs for treatment of angina," the researchers were quoted in the British medical journal. After four weeks on the drug, 26 exercise test patients showed no symptoms, and the researchers saw very few side effects.

Diltiazem from Marion Laboratories is a Japanese drug and most of the work with it has been done in Japan, where it has been marketed since 1974. There is

very little data in American literature.. The drug is given orally and—like others in its class—it may be given concomitantly with nitrates or other drugs. A Texas team reported results of a study conducted on differential effects of diltiazem and verapamil in conscious dogs, showing both drugs produced a 68 percent increase in heart rate and a similar decrease in mean arterial pressure, but cardiac output increased by 86 percent with diltiazem and only 68 percent with verapamil.

Perhexiline maleate from Merrell National Laboratories, the fourth drug in the study, is not perceived as a first-line antianginal agent because of its side effects—dizziness, ataxia, and impaired liver function. There are many reports of the compound's efficacy, however, and it may be used in patients not responsive to the other agents.

The changing concept of cardiac disease does not pick one situation—spasm or atherosclerosis—and lay all cardiac ills on it. Cardiac specialists recognize that some persons have straightforward atherosclerosis without spasm; some have spasm and normal blood vessels; and others have a combination of the two conditions. But doctors are pleased with the discovery of spasm's importance because, with the development of the calcium antagonists, there's something they can do about it, while they were helpless against atherosclerosis. The calcium antagonists promise more specific therapy for a condition that is both medically serious and terribly frightening to the patient.

DRUG TOPICS magazine is published twice monthly by Medical Economics Co., a division of Litton Industries, Inc., which also publishes a group of journals, annuals, books, and compendia for the healthcare professional.

AMA NEWS:

HEALTH IMPROVES

Physicians and other health care professionals were gratified to learn in 1980 that they are doing many things right. Early in the year came a report from the federal government listing clear progress in extending health resources and in reducing premature and preventable deaths. Officials viewed the

health improvement in the past 10 years as an almost revolutionary development with far-reaching implications.

Life expectancy at birth in 1980 was up to more than 73 years, while infant mortality was down to no more than 12 per 1,000 live births. These two statistics often are cited in evaluating a nation's health care system. Both are setting new records year after year as people live longer and more infants survive the experience of birth.

Calculations at Stanford University this fall indicated that average Americans in the not-too-distant future can expect to live to a vigorous, active and productive 85 years. There will be few deaths in youth or middle years in another generation. White women are almost there, with a life expectancy of 78 years today. Of course many people always live far beyond the stated "norm."

PROBLEMS THAT REMAIN

Despite progress, no one — especially physicians — was fully satisfied with the state of the nation's health. The president of the American Public Health Association pointed to the health hazards of the environment, particularly polluted air and water, as problems that remain to be solved. Safe disposal of toxic chemical waste assumed proportions of a major national health problem as more Love Canal situations were uncovered across the nation in 1980.

And there still were Americans whose access to health care could be improved. The task of health education to motivate people to live a truly healthier life was formidable. Chicago newspapers published editorials titled "Parents Who Don't Care" in reporting that after five months of intensive health education efforts 40 percent of pupils had not received their required immunization shots at the opening of school. It took a massive crash program to reach the unvaccinated.

Health manpower continued to be debated in 1980. The health care community was almost desperate for more nurses, and many areas still needed doctors. But a federal government study predicted that the end of the doctor shortage (if there is one) is in sight, that in another 10 years there will be a surplus. The medical education community should cut

back on enrollment in medical schools, the panel declared. The medical community promptly cautioned that this recommendation may be unfounded.

Steadily rising costs of health care continued during 1980 to plague the health care community. Physicians and hospitals continued their voluntary effort to contain the rate of increase. But inflation in the general economy hit the health care community as well, and costs continued to rise. Various proposals were aired to curb cost escalation, but nothing drastic happened in the cost area in 1980. Everyone agreed that costs should be contained, but no one was exactly sure how to do it intelligently.

DIET AND NUTRITION

In the all important field of diet and nutrition, a fresh element of common sense surfaced in 1980 with issuance of new guidelines by the Departments of Agriculture and Health, Education and Welfare (now Health and Human Services). They recommend: Eat a variety of foods, including foods with adequate starch and fiber; maintain proper weight; avoid too much fat, saturated fat and cholesterol, and too much sugar and salt; drink alcohol only in moderation.

The new guidelines quit trying to set specific quantity recommendations — a certain portion of one's diet should come from fat, for example. Still, there was criticism of the "eat-less-of-this-and-avoid-too-much-of-that" dietary advice, as being unrealistic, unnecessary and unworkable. Nutritionists continued to point to the virtual absence of nutritional disease in the United States today as clear evidence that the American diet is not all that bad.

The health scare of the year was Toxic Shock Syndrome. All at once millions of American women who used tampons during menstruation read in their newspapers and heard on the air that these useful little devices were blamed in a serious illness. One brand of tampons was withdrawn from the market. Experts issued guidelines recommending use of less absorbent types, frequent changing of the tampon, and switching to pads a part of each day.

There were only a few hundred cases of Toxic Shock Syndrome reported in the entire nation, but a major health scare was created, and was still a factor

at the end of the year.

MAJOR HOPES

The medical research hope of the year was interferon. Interferon is the body's own mechanism of resisting infection and disease. At year's end efforts were under way in a number of large laboratories to produce interferon in enough quantity to conduct large scale human tests to determine whether it is effective against cancer, and possibly against many virus diseases. Small scale preliminary tests have shown promise.

Laboratory production of interferon is made possible through one of the more sensational research advances of this generation, gene splicing. It's complicated and difficult to understand, but a big segment of the public in 1980 became aware that science now knows how to go into gene structure and rearrange them in a favorable manner.

The technique is known as Recombinant DNA, and many scientists feel strongly that it may open up an entire new field to science. Interferon still is largely unproved, and the physician in his office does not have access to a supply for his patients.

Large commercial units were involved in the potentials of producing interferon and other possibilities stemming from Recombinant DNA. Harvard University considered, and finally rejected, a proposal to form a corporation and go into the business. Stock prices boomed when a West Coast commercial firm working with Recombinant DNA went public.

Another great research hope of 1980 was a natural substance in the brain — beta-endorphin. Scientists sought to learn how the endorphins worked to effect human emotions and to ease pain. They have shown promise in treating depression and schizophrenia. The endorphins look promising, but there still is much more to be learned.

CANCER THERAPY

In cancer, drugs are curing more patients now than ever before, interferon is the hope of the future, and steady progress continued in 1980. Survival rates improved for many of the most common forms

of cancer. Cancers of the uterus, cervix, breast, colon, rectum, prostate and bladder are slowly yielding to treatment. Cancer mortality dropped among Americans under age 55.

The cure rate continued to be promising among children with leukemia, and was running as high as 80 percent in childhood lymphoma.

The tragic final illness and ultimate death of Film Star Steve McQueen underscored dramatically the still widespread belief in unproved and unconventional cancer therapies. Americans still were patronizing "clinics" across the Mexican border to partake of laetrile, coffee enemas and rub downs with castor oil in futile efforts to cure their cancer.

The American medical community had a word of advice to those facing apparently terminal cancer regarding the Mexican clinics and their offshoots — "Save your money." Your surviving family will need it, and the treatment won't do you any good. Perhaps McQueen's death will be a warning signal to Americans to shun the unproven therapies.

TOP MEDICAL STORIES

A brief rundown of some of the medical news stories of 1980 follows:

A Canadian researcher in the relatively new science of chronobiology found that Monday is the most dangerous day in the week for men to die of heart attack. Perhaps it's the stress of the return to work after a weekend.

The once-controversial CAT scanner — cited frequently as an example of the high cost of modern medical technology — proved itself in 1980, with findings that it actually saves money when used to guide the radiation treatment of cancer.

The public read with much interest a suggestion that children were less likely to choke on flat hot dogs than on round ones, but at year's end the nation still was consuming round hot dogs. And no flat ones were in sight.

Major improvements in the health care of American Indians were noted in a report in the fall. Disease rates were dropping and infant deaths were much less common. Some of the credit went to the physicians recruited by the American Medical Association

for Project U. S. A. These men and women served for short periods in the Indian Health Service and the National Health Service Corps to relieve the regular physicians for vacations and opportunity to participate in continuing medical education courses. There was a return also to cooperation with the Indian medicine men. Modern doctors found that these folk practitioners could teach them something about getting well.

SKI INJURY ANALYZED

Skiers were interested in a study which found that their new-type runaway straps (holding ski to boot in event of a fall) actually were causing the ski tips to fly up and hit the skier in the face. Switching to a simple braking device could correct the problem.

Literally millions of families plagued by nighttime snoring of one of their members read with interest of a new approach — wear a cervical neck collar in bed, to prop up the chin and keep the airways open, thus curbing snoring.

Middle-age men were advised not to fear dropping dead on the tennis court or during other strenuous exercise. This happens only to those who already have far advanced heart disease, said a Dallas researcher.

Women were offered hope for better control of menstrual cramps, in a report evaluating new medications now available, prostaglandin inhibitors. These have proved effective in some trials.

Asthmatic athletes were given encouragement by a study that discovered they can forestall an attack of exercise-induced asthma, particularly in cold weather, by wearing a simple surgeon's gauze face mask.

The federal government, the AMA and others warned several times during the year of potential health hazards from the proliferating sun tanning parlor across the nation. Tanning is bad for the skin, whether from sunlight or from lamps.

DOG BITES BOOM

Dog bites have become a major health problem in the United States, with more than one million reported bites each year and probably countless others unreported.

Near-sighted Americans (of which there are

many millions) were intrigued by reports of a new eye operation purported to correct this vision problem. But America's eye specialists this fall urged caution. The operation still is far from proved. It's called radial keratotomy, and involves a series of tiny cuts into the eyeball. Most eye doctors advise glasses rather than surgery.

A new rabies vaccine was confirmed in 1980 as safe and effective. The new vaccine requires only five shots, instead of the 21 shots needed of the old vaccine.

Organ transplants continued. Kidney and cornea transplants were widespread. Only a few heart transplants still were being done. Liver transplants struck a snag for a time, but had been resumed at the year's end.

The AMA issued, for guidance of physicians, a new book, *Laboratory Tests in Medical Practice*. In preparing the book, the AMA's consultants determined that laboratory medicine as now practiced in the United States is more advanced and of better quality than in any other nation in the world.

The Los Angeles County Medical Society stepped in with enough money to rescue the city's Poison Information Center, a valuable data source about poisoning for doctors all over the world. The Center had been about to close for lack of funds.

SMALL TOWNS GET DOCTORS

Whether or not there is a shortage of physicians, one expert in management of medical practice reported that physicians are beginning to move into small towns and hamlets, many of which haven't had doctors for years. Practice opportunities are fewer in the larger cities and their suburbs, and doctors are beginning to head back to the small towns.

Senility in advancing years can be relieved often by medical treatment, a government task force found. Normal aging does not include gross intellectual impairment, confusion and delusions, the group declared.

The battle on smoking continued in 1980. And the Journal of the AMA published a report pointing out that snuff and chewing tobacco, being promoted as alternatives to smoking, also are dangerous to your health.

Nonsmokers are adversely affected by tobacco smoke, a California research project found. Nonsmokers working in a closed environment with smokers had a significantly reduced breathing capacity when compared to nonsmokers not exposed to cigarette smoke. And a Surgeon General's report declared that women are catching up with men in lung cancer, as the ratio of men vs. women smokers evens off.

Emergency medicine specialists learned during 1980 that drowning victims may be successfully revived after 20 minutes or more under water, if the water temperature was quite cold. Icy cold water extends the survival period, previously thought to be no more than five minutes.

LUNG DISEASES

Disabling occupational lung diseases of coal miners, asbestos workers, textile workers, quarry workers and others occupied much attention in public health circles in 1980. There was no question that these occupations had some affect on the lungs of the workers. But some experts declared that only when combined with cigarette smoking were these conditions actually disabling.

Legionnaires' Disease, much in the news a few years ago, was becoming routine and no longer created a panic. Ohio scientists said the death toll may be as much as 70,000 Americans annually from unrecognized cases of Legionnaires's Disease.

Nutritionists from the Americas gathered in the late summer at Los Angeles for the triennial Western Hemisphere Nutrition Congress. Overeating and obesity proved to be a major nutritional problem for North Americans. Latin Americans reported progress in providing better diets for their peoples.

The enzyme chymopapain once again was found effective in relieving back pain from slipped disc, but still was unproved to the satisfaction of the U.S. Food and Drug Administration. Americans were going to Canada for chymopapain treatments.

JOGGERS GET ADVICE

A host of medical advice for joggers continued to appear in the medical journals and in the public

press. A Canadian researcher offered pointers for avoiding heat stroke while jogging — take plenty of fluids, run in the early morning or evening on hot days, slow down speeds in hot weather.

Some couples were opting for having their babies at home rather than in the hospital. But obstetricians still preferred to handle deliveries in hospitals, or at least in birthing centers, where support facilities are available should unforeseen problems occur.

Further studies confirmed that THC, the active ingredient in marijuana, is helpful in controlling nausea in cancer patients receiving strong medication. It isn't necessary to smoke the weed. The THC is extracted and given in capsule form.

The millions of American men, particularly older men, who suffer from sexual impotence read with interest last winter a report that there often is a physical cause for impotence, and that treatment might help. Harvard Medical School studies found that erectile potency depends on a healthy psyche, but also on neurological, vascular and hormonal systems functioning properly.

PRINCIPLES OF ETHICS

The AMA updated and revised its Principles of Medical Ethics for physicians in the summer of 1980. The new version clearly restates existing policy on advertising, and the relationship of physicians with limited-license practitioners. The revised Principles reflect the Association's response to modern social reality.

The coronary bypass operation remained controversial in 1980. Some said it is not worth the cost and effort. Others strongly endorsed it. A Milwaukee study found that coronary bypass surgery permits many men to continue to work who previously would have been cardiac cripples.

Is the current fad for saunas and hot tubs doing anything for our health? Not much. The main value of the heat treatment, said an Illinois doctor, is that it feels so good when you quit.

An extremely large chunk of the American population is overweight, and the percentage is growing year by year. One ray of solace for the fatties came in a report last spring declaring the height-weight tables held up as the American norm are probably

much too low, that Americans don't have to be as skinny as the tables say to be in good health. But there's no doubt that true obesity is a health risk.

New findings continued to appear in 1980 on the subject of estrogen use by women during menopause to relieve the discomforts and remain feminine. California researchers determined that estrogen use by postmenopausal women increases risk of breast cancer, if continued for several years.

DMSO caused a stir toward the year's end. This purported panacea for everything still is licensed for medical use for only one limited ailment, bladder cysts. But it is being pushed outside medical circles as treatment for arthritis. Possible side effects still are unknown.

Test tube babies still commanded press interest, but there was little activity. U. S. efforts had not produced a fetus by late in the year. This technique for enhancing fertility still is far from perfected.

The 1980 Nobel Prize in Medicine was won by two Americans and a Frenchman for research that led to discoveries about how the structure of cells relates to diseases and organ transplants. The three are Dr. Baruj Banerjee of Harvard Medical School; Dr. George C. Shell of Jackson Laboratory at Bar Harbor, Maine, and Dr. Jean Dausset of the University of Paris.

SE VENDE

Apartamento Condominio Generalife, Avenida San Patricio, Guaynabo. Cuarto piso, completamente decorado y equipado; 3 habitaciones; aire acondicionado central en 2 unidades individuales — Incluye 2 parkings para automóviles-protegidos por portones eléctricos - Piscina - Area de juegos.

Llamar al Dr. Rafael A. Nieves:

Oficina — 725-0909

Residencia — 792-2052

Radio Call — 755-3050 - Radio - 3276

Health and Safety Tip

From the American Medical Association

535 North Dearborn Street/Chicago, Illinois 60610

Glaucoma Often Undetected in U.S.

Glaucoma Hits Many

In the United States alone, about 800,000 cases of glaucoma are undetected.

Glaucoma, a rapidly destructive eye disease, is characterized by high pressure within the eyeball, says a booklet from the American Medical Association.

This pressure causes deterioration of the optic nerve and can lead to blindness. The latest figures show that 12 per cent of all blindness in the United States results from glaucoma. With proper medical treatment, however, visual damage can be prevented.

Common forms of glaucoma usually are found during a routine eye examination because symptoms are often not present. Blurring of vision, especially if the disease worsens and spreads, indicates that the disorder is well underway.

Glaucoma occurs most often in patients more than 40 years old and is occasionally inherited. Patients in this age group, especially those with a family history of eye disease, who suffer repeated symptoms of aching or discomfort of the eye without satisfactory relief from eyeglasses, should have a glaucoma test. The test measures pressures within the eyeball by means of a tonometer, a device that, when pressed on the anesthetized cornea, registers the pressure within the eye.

If the tonometer shows a high reading, which is an indication of glaucoma, further testing is done with a gonioscope. This device consists of a mirror or prism and contact lens and is used for viewing the angle of the eye chamber where the cornea and the iris are joined. In this way, the examiner can determine what type of glaucoma a patient has. Other vision tests also will be done.

Glaucoma can be treated by medications prescribed by a physician. Surgery is used only in a relatively few advanced cases.



November, 1980
Frank Chappell
Science News Editor
AMA

In G.I. therapy



Adjunctive Librax[®]

Each capsule contains
5 mg chlordiazepoxide HCl
and 2.5 mg clidinium Br

antianxiety/antisecretory/antispasmodic
for adjunctive therapy of duodenal ulcer*
and irritable bowel syndrome*

Librax

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Possibly effective as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis, and acute enterocolitis).

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma, prostatic hypertrophy, benign bladder neck obstruction, hypersensitivity to chlordiazepoxide HCl and/or clidinium Bromide.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery or driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librax[®] (chlordiazepoxide HCl/Roche) to known alcohol-

tion-prone individuals or those who might increase dosage, withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially, increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug.

and oral anticoagulants, causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated, avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction, changes in EEG patterns may appear during and after treatment, blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, i.e., dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other osmolytics and/or low residue diets.

ROCHE

Roche Products, Inc.
Manati, Puerto Rico 00701

α

Alpha Stimulation

Central Control of
Blood Pressure*



*The Family of Man" by Roberto Moretti,
a statuary in crystal symbolizing the broad range of
hypertensive patients eligible for therapy with Catapres

The Alpha Advantage:

It's for all kinds of hypertensives

- Unlike beta blockers, Catapres® has no contraindications.
- Catapres can be useful even in these patients with:

Congestive heart failure	Allergic rhinitis
Ventricular hypertrophy	Hepatic disease
Hyperglycemia	Hyperuricemia
Diabetes mellitus	Gouty arthritis
Bronchial asthma	Sulfonamide hypersensitivity

Like any antihypertensive, use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

work/play—normal hemodynamic responses to exercise maintained.

love—low incidence of impotence and/or loss of libido:
2.8% in 1,923 patients studied.¹

cardiac output—tends to return to control values during long-term therapy.

blood flow—preserved in kidney.

No Single Advantage Determines Drug Choice.

Other factors must include:

The drug's effectiveness in a given patient, its side effects, warnings, precautions, tolerance, etc. A rational therapeutic choice depends on a careful assessment of all such factors.

* Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

¹ Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

**Now available in new
0.3 mg tablets**

Tablets of 0.1, 0.2, 0.3 mg
Catapres
(clonidine HCl)
Hypertension

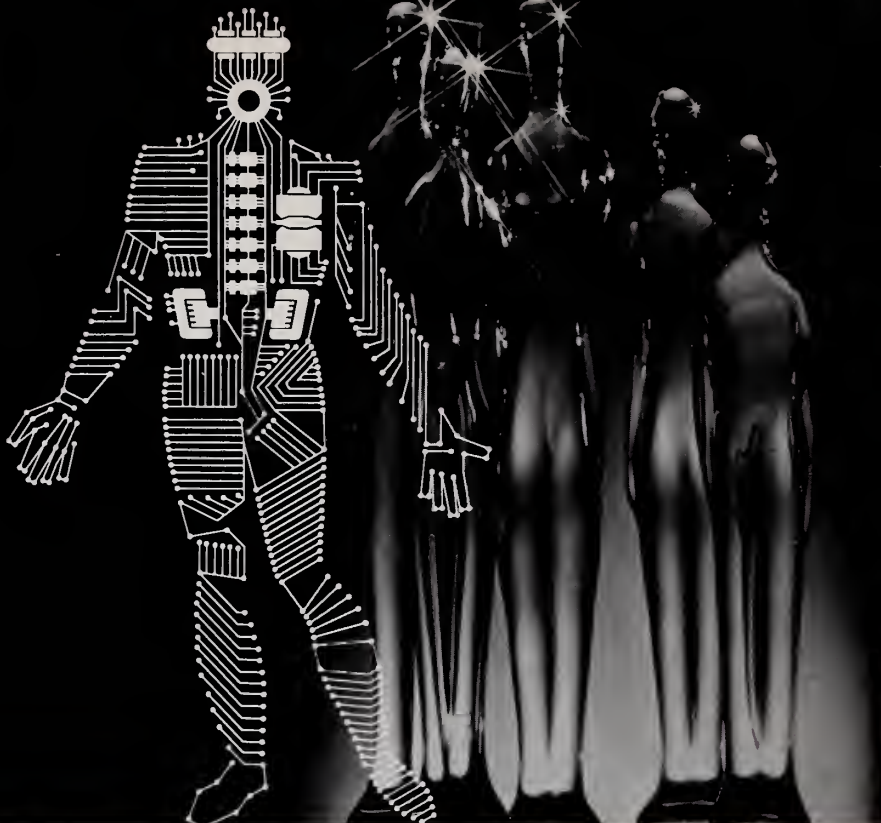




The Alpha Advantage:

It's for all kinds of hypertensives

Tablets of 0.1, 0.2, 0.3 mg
Catapres
(clonidine HCl)
Hypertension



- No contraindications.
- Effective in all degrees of hypertension. It is mild to moderate in potency.
- Low incidence of depression, impotence, orthostatic hypotension—no fatal hepatotoxicity.
- Preserves kidney blood flow.

Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1, 0.2, 0.3 mg

Indication: The drug is indicated in the treatment of hypertension. As an anti-hypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of

The usual starting dose of Catapres is 0.1 mg at breakfast and 0.1 mg at bedtime. Some patients may benefit from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg
Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chloralhydrate and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecostasia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000. Also available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.
Under license from Boehringer Ingelheim GmbH



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Ridgefield, CT 06877**

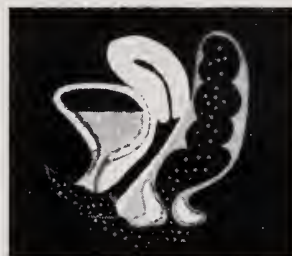
ROCHE

For recurrent attacks of urinary tract infection in women

Bactrim™ DS Double Strength Tablets

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Just one tablet b.i.d. for 10 to 14 days



- Action at urinary/vaginal/lower bowel sites helps eliminate reservoirs of infecting organisms
- Distinctive antibacterial action plus wide spectrum helps eradicate recurrent UTI
- Low incidence of bacterial resistance in community practice

- Convenient *b.i.d.* dosage provides day-and-night antibacterial control
- Contraindicated during pregnancy and the nursing period. During therapy, maintain adequate fluid intake; perform CBC's and urinalyses with microscopic examination.

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. **Note:** The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

The recommended quantitative disc susceptibility method (*Federal Register*, 37:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers; infants less than two months of age.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. **Blood dyscrasias:** Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. **Allergic reactions:** Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. **Gastrointestinal reactions:** Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. **CNS reactions:** Headache,

peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. **Miscellaneous reactions:** Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

Urinary Tract Infections: Usual adult dosage—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Recommended dosage for children—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

***Pneumocystis carinii* pneumonitis:** Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: Double Strength (DS) tablets, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, Tel-E-Dose® packages of 100. Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. Oral suspension, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).



Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Please see back cover.

1327 078

Her next attack of cystitis may require

the Bactrim[™] 3-system counterattack



ROCHE

Bactrim has shown high clinical effectiveness in recurrent cystitis as a result of its wide spectrum and distinctive antimicrobial action in the urinary, vaginal and lower intestinal tracts.

The probability of recurrent urinary tract infection appears to be enhanced by the establishment of large numbers of *E. coli* or other urinary pathogens on the vaginal introitus. The trimethoprim component of

Bactrim diffuses into vaginal fluid in effective concentrations, thus combating migration of pathogens into the urethra.

Studies have shown that Bactrim acts against *Enterobacteriaceae* in the bowel without the emergence of resistant organisms. Thus, Bactrim reduces the risk of introit colonization by fecal uropathogens. It has no significant effect on other normal, necessary intestinal flora.

Bactrim fights uropathogens in the urinary tract/vaginal tract/lower intestinal tract

Please see reverse side for summary of product information.

